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SYNOPSIS

The pathological physiology of duodenal ulcer in general is discussed in Chapter I. The current views regarding the role of the antrum and the vagus nerves and their interrelationship are discussed briefly.

In Chapters II and III the experimental procedures used for the production of peptic ulcer are reviewed. In Chapter IV a new method for the experimental production of peptic ulcer is described. This method was devised in our laboratory and offers several advantages over those previously described. This procedure consists of interposing a segment of terminal ileum isoperistaltically in the first portion of the duodenum. This resulted in large deep callous ulcers in the ileal segment in seven of the nine dogs.

In Chapter V the current surgical procedures used in duodenal ulcer therapy are critically appraised. Physiological considerations and postoperative problems of the individual operative procedures are discussed briefly.

The final chapter deals with the results and conclusions of our experiment. The new procedure for the experimental production of peptic ulcer has been performed in conjunction with nineteen of the standard procedures for the surgical treatments of duodenal ulcer, ninety dogs being used with three to eight dogs in each group.

With the exception of complete excision of the gastric mucous membrane, none of the presently employed procedures for duodenal ulcer completely protected the animals against the development of ulceration. There was, however, a significant difference in the incidence of ulceration following the various procedures.

A study was also made of the effect of vagus section, antrectomy and excision of the acid secreting mucosa. With respect to both antrum and vagus the animals are less likely to develop a peptic ulcer if the vagus is

divided and the antrum is removed. With respect to the vagus this must imply that its acid stimulating effects are greatly in excess of its inhibiting effects. With respect to the antrum the same is true, particularly if the antrum is innervated.

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THE UNIVERSITY OF ALBERTA

" THE EVALUATION OF CURRENT DUODENAL ULCER SURGERY BY THE USE OF A NEW EXPERIMENTAL METHOD OF ULCER PRODUCTION. "

A Thesis

Submitted to the Faculty of Graduate Studies

in Partial Fulfilment of the Requirements for the Degree

of Master of Science

in the

Faculty of Medicine,
Department of Surgery,
University of Alberta,

by

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INTRODUCTION

Peptic ulcer has attracted the attention of men in several of the special fields of medicine. The surgeon is most interested because few fields have offered greater opportunities for the exercise of his ingenuity in devising different operative procedures for cure or relief, and few patients are more grateful than those with ulcers when relief is obtained.

However, a review of the voluminous current literature on peptic ulceration and its experimental production reveals that few factors concerning the lesion go unchallenged. Dr. Wangensteen has said that a man could spend the rest of his life reading the research work that has been done on the subject of peptic ulceration.

The anatomical, physiological and pathological factors responsible for the lesion are widely debated. The rapidly changing procedures employed by surgeons in treating ulcers prove that no one method has been wholly satisfactory. Experimental ulcers have been produced by many surgical and chemical methods. None have proven to be entirely satisfactory for the study of all phases of the ulcer problem in man. Peptic ulceration is thus a problem with many unsolved facets.

CHAPTER I

PATHOLOGICAL PHYSIOLOGY OF DUODENAL ULCER

I. INTRODUCTION

Unfortunately the etiology of peptic ulceration is unknown at present. It is true, however, that peptic ulcer does not occur in the human in the absence of hydrochloric acid and pepsin. Irrespective of the methods used one finds an increased duodenal acidity and an increased production of acid by the stomach in patients with duodenal ulcer.

II. CONTROL OF ACID PRODUCTION BY THE STOMACH

Cephalic Phase

By this phase stimulation or inhibition of gastric secretion results, mediated by the vagi. The vagus nerve constitutes the entire cranial outflow of the parasympathetic nervous system in the abdomen, and contains both stimulating and inhibiting fibres. Both the secretory and motor effect of the vagus on the stomach can be duplicated by acetylcholine and other cholinergic drugs. Wolf and Wolff[231] demonstrated that emotional states can influence gastric secretion, and the response is not always predictable. For example anger inhibited secretion on some occasions, and at other times increased secretion.

Gastric Phase

This is now called by some the antral phase of gastric secretion. The distention of the antrum or the presence of food in the antrum results in the production of gastrin, which stimulates parietal cells to secrete acid[50].

Intestinal Phase

Food products or possibly a humoral agent similar to gastrin are absorbed from the proximal intestine, which stimulates gastric secretion[105]. Kosaka and Lim[113] demonstrated that the inhibition of gastric secretion following a fatty meal was due to the formation of a humoral agent (enterogastrone).

Carlson[27] found in his gastric fistula subjects that approximately 20% of the daily secretion of gastric juice was due to the nervous phase. Animal experiments suggest that the cephalic and gastric phases are each responsible for 45% of gastric secretion, whereas the intestinal phase is responsible for only 10%[183]. The adrenal, pituitary and pancreas may play some role in the control of acid secretion, but it is relatively minor in comparison to the cephalic and gastric phases[221]. Their relation to peptic ulcer will be discussed under the role of endocrines.

III. THE ROLE OF THE VAGUS

In 1814 Brodie demonstrated that the vagi exercise control over gastric secretion. He concluded that suppression of secretion could be attributed solely to division of the vagus nerves. It remained for the classic experiments of Pavlov, reported in 1889, to establish beyond question the role of the vagi in gastric secretion. He prepared a dog with a cervical esophagotomy and gastric fistula. When the animal was fed, ingested food escaped through the opening in the neck and did not enter the stomach. Pavlov called this "sham feeding" and it was followed within five minutes by a copious flow of highly acid gastric juice from the gastric fistula. After section of the vagi the animal sham fed as readily as before but no gastric secretory response was obtained. Dragstedt[40]

developed a technic for isolating the entire stomach of the dog with preservation of its vagal innervation. The nervous phase was more prominent in this preparation than the antral phase.

The nervous mechanism in man was first described by Carlson[27] in 1916 in a subject with a lye stricture of the esophagus and a surgically created gastric fistula. Mastication of palatable food caused the typical "sham feeding" response in this patient, but the sight or smell of food was observed to have little effect. Captain Beaumont recognized the unique opportunity which St. Martin's misfortune provided for direct observation of gastric physiology in man, and he was able to record many important facts which remain unchallenged to this day. Beaumont recorded only a few observations about the mechanisms and nature of gastric secretion per se; his major interest centred upon gastric digestion.

The nervous mechanism of gastric secretion can be readily activated by insulin induced hypoglycemia[199]. The response is completely abolished by vagotomy and can therefore be used as a test for the presence of vagal innervation to the stomach in both man and the experimental animal.

In 1944 Dragstedt and his co-workers[41] reported that an excessive continuous secretion of gastric juice occurred in patients with duodenal ulcer, and that this was reduced to normal or subnormal levels by division of the vagus nerves just above the diaphragm. Basal gastric secretion was studied in human subjects by the introduction of a nasogastric tube and continuous aspiration during a nocturnal twelve hour period with the patient in the fasting state shielded from sight and odor of food[114]. This was further confirmed and extended by Levin[119] who found that patients with duodenal ulcer secreted approximately four times as much hydrochloric acid in the basal state as did normal individuals.

Clinical experience has suggested that the hypersecretion associated with duodenal ulcer is of nervous origin. Firstly, the etiology of the disease indicates the importance of occupation and situations provoking emotional and nervous tension. Secondly, the hypersecretion is abolished by vagotomy and is reduced by anticholinergic drugs, and lastly the stomach of a patient with duodenal ulcer contains an excessive number of parietal cells. Whether this increase in parietal cells is cause or effect is unknown[209].

IV. THE ROLE OF THE ANTRUM

Edkin[51] in 1906 first postulated that the antrum of the stomach might elaborate a hormone, which mediates the gastric or antral phase of gastric secretion. He reported that the intravenous administration of antral mucosa extract stimulated gastric secretion. In other studies the introduction of food substances into the antrum also was followed by the stimulation of acid gastric juice. Edkin's observations were followed by four decades of controversy concerning his gastric hypothesis. The experience of surgeons with the antrum exclusion operations seemed to confirm Edkin's view. The problem was reinvestigated by Dragstedt[43] using the pouch collection technic and he was able to assemble reliable quantitative data in its favour.

a) Effect of antrum ablation on gastric secretion

Studies on Pavlov pouches showed resection of the gastric antrum resulted in an extensive reduction (65 - 95%) of acid gastric juice [233]. It was apparent that the major stimulus responsible for the secretion of acid gastric juice by these isolated pouches was in some way related to the presence of the antrum.

b) Effect of antrum transplantation on gastric secretion

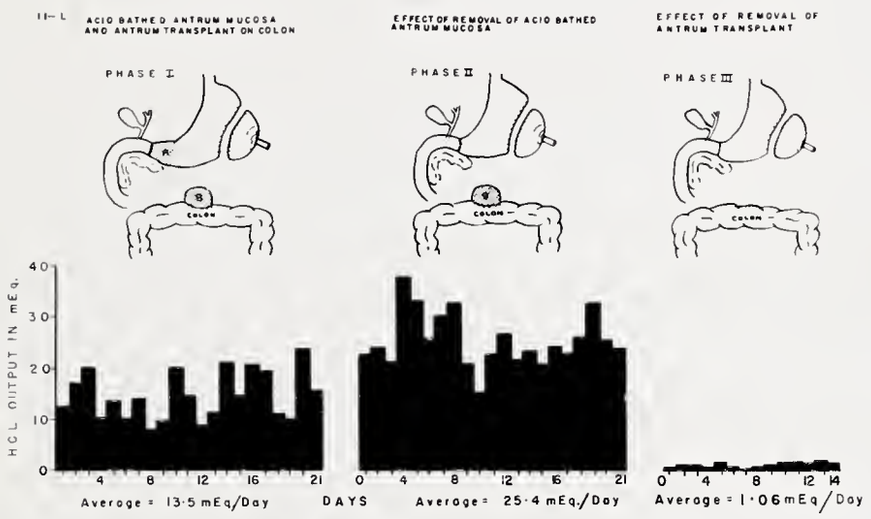
The antrum was removed from gastrointestinal continuity and reintroduced by stages into the second part of the duodenum or colon[43]. The results demonstrated that even after complete interruption of the extrinsic nerve supply to the antrum and separation of the vascular and neuromuscular connections that it was capable of stimulating powerfully the body of the stomach to secrete acid gastric juice[219, 66]. This was particularly marked if the antrum was connected to a portion of the gastrointestinal tract whose pH was alkaline.

c) Acid inhibition of the antrum

It has been proven clinically and by experimental methods that the introduction of acid (e.g. 5% HCl) into the stomach, duodenum or isolated antrum suppressed further acid formation[232, 234, 60]. Sokolov[189] first observed that acid in the region of the antrum inhibited secretion by the fundic cells.

If, after making a Heidenhain pouch the antrum is transplanted into the colon (Fig. 1), it no longer comes in contact with acid secreted by the body of the stomach. The result is a threefold increase in secretion of acid gastric juice by the pouch, indicating that the gastrin mechanism is held in check in its normally acid environment[43, 115]. Other studies have shown that any operative procedure that will reduce gastric acidity, such as vagotomy or gastroenterostomy will result in an excessive release of gastrin[54]. The isolated innervated antral pouch constructed with a double mucosal barrier is highly susceptible to chemical stimuli and also responds to mechanical distention[232, 238]. The pH of the gastric content can be considered to constitute an autoregulatory mechanism. When the pH falls to approximately 1.5 the gastric phase of gastric secretion is terminated.

FIGURE I



The effect of antrum transplantation on gastric HCl secretion.

The mechanism by which acid inhibits the antrum remains a subject of some controversy. The experiments reported by Harrison et al[93] from our laboratory, illustrated by Figure I, suggest that the antrum is capable of producing an inhibitory hormone. This was confirmed by Jordan and Sand[107], but not confirmed by others[120, 44].

d) Relationship between antrum and gastric ulcer

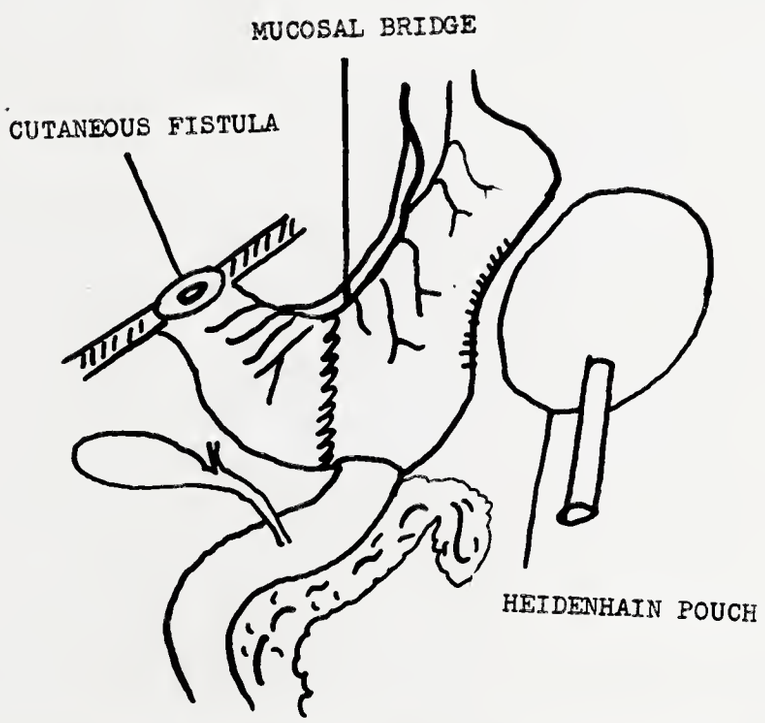
Clinical studies show that basal secretion and motility is less than normal in gastric ulcer patients[45]. Dragstedt stressed the importance of gastric retention in gastric ulcer and reported that 7 out of 150 duodenal ulcer patients treated by vagotomy alone developed gastric ulcer[43]. In the dogs prepared with Heidenhain pouch division of the vagus nerves to the remaining portion of the stomach caused a marked increase in gastric acid secretion by the pouch[190]. This effect does not occur if the antrum has been previously resected or if stasis in the stomach is prevented by a surgical drainage procedure. It is apparent, therefore, that the gastrin mechanism is affected by hypomotility and gastric retention associated with vagal denervation. Gastric retention associated with anastomotic narrowing at the pyloric outlet also exaggerates the gastrin mechanism and is associated with gastric ulcer[57, 135]. In dogs prepared with a Heidenhain pouch pyloric obstruction results in an increase in pouch secretion, and they often develop gastric ulceration[178]. These observations indicate the importance of the antrum in gastric ulcer. It is also interesting to know that in man almost all gastric ulcers occur in the mucosa of the antrum or in the zone of separation between antrum and the acid secreting body of the stomach[152].

V. INTERRELATIONSHIP OF CEPHALIC AND GASTRIC PHASES OF GASTRIC ACID SECRETION

In 1915 Schur and Plaschkes[191] first suggested a possible relationship between the cephalic and gastric phases of acid secretion. Uvnas[212] later presented the concept that the cephalic phase of gastric secretion is controlled by a combined neurohumoral mechanism. He concluded that a secretagogue agent was released from the pyloric region during vagal stimulation which potentiates the direct effect of the vagus upon the parietal cells. Further work was done by Lim and Mozer[121] in 1951 who showed that sham feeding in esophagostomized dogs with a gastric fistula produced a gastric secretory response greater than the vagal phase alone. They suggested the possibility of peripheral liberation of gastrin. However, these authors were unable to demonstrate increased acid secretion from denervated fundic pouches after isolation of an innervated antral pouch and sham feeding.

This subject was also investigated by Dragstedt[153] and others[121]. He fashioned a vagally innervated isolated antrum separated from the main stomach by a double mucosal bridge with the pyloric end brought out to the skin fistula (Fig. 2). Thus the antrum was removed from local, chemical or mechanical stimuli, and changes in gastrin release of vagal origin were studied by a Heidenhain pouch. Using this method he demonstrated the release of gastrin by insulin hypoglycemia. Thein and Schofield[210] were able to demonstrate much increased acid secretion from denervated pouches during sham feeding when the innervated antrum was isolated. In view of these experiments it can be concluded that vagal stimulation does release the hormone gastrin and the two major phases of gastric acid stimulation are interrelated.

FIGURE 2



EXCLUSION OF THE GASTRIC ANTRUM WITH INNERVATION INTACT

Exclusion of the gastric antrum
with innervation intact.

The exact mechanism for the release of gastrin is unknown; however, it would appear that vagal stimulation of the antrum can result in the release of gastrin. It has also been shown that gastrin release by vagal stimulation is independent of gastrin release stimulated by antral distention or the presence of food in the antrum[219].

Devito et al[49] demonstrated that after antroneurolysis there was a 20 - 80% drop in 24 hours in Heidenhain pouch secretion. This depression in acid secretion is probably due to removal of the vagally induced gastrin production, as this depression is not affected by local, chemical and mechanical gastrin release mechanisms[238]. The rise in acid secretion from a Heidenhain pouch following isolation of an innervated antrum indicates that the antrum is releasing gastrin via the vagus in the absence of local antral stimuli and in the absence of acid inhibition.

Considering the role of the antrum and vagus, Nyhus et al[149] recently suggested a new terminology for the stimulating phases of gastric acid secretion replacing Pavlov's old classification. These are as follows:-

1) Direct vagal	Neural (conditioned and unconditioned reflexes)
2) Vagal antral	Neurohumoral
3) Local antral	Humoral
4) Intestinal	Humoral

It is difficult at present to evaluate clinically the role of the innervated versus the denervated antrum.

VI. REGULATION OF THE ACIDITY OF THE GASTRIC CONTENTS

Most investigators agree that hydrochloric acid or its precursor is the product of the secretory activity of the parietal cells. Hydrochloric acid appears in gastric juice in two forms, free and bound. That portion of acid which combines with hydroxyl ions or with a protein

molecule is called "bound acid", and this does not take part in the genesis of peptic ulcer[6]. On the other hand, the quantity of free or unbound acid is intimately related to the cause of duodenal ulcer and probably also gastric ulcer. Ninety percent or more of the total acid secreted comprises free hydrochloric acid. Thus it is that free acid must be neutralized, buffered, or diluted, if acid - peptic digestion of the mucosa is to be prevented.

The acidity of the mixed gastric contents results from the following factors[20]: -

1) The rate and quantity of parietal cell secretion regulated by the various physiological mechanisms already discussed.

2) Alteration of parietal secretions occur by

a) Emptying of the stomach

or

b) The back diffusion of acid and water into the blood across the gastric mucosa. Teorell[20] has advanced his theory, supporting the mechanism of back diffusion across the gastric mucosa. To quote from Babkin[20] - "The gastric juice is secreted mainly as pure HCl and simultaneous inward diffusion of NaCl - strictly speaking an ionic exchange between H and Na. The reduction in acidity and variation of amount of chloride takes place in this manner."

Engostrom's theory[20] explains further that the back diffusion of the H ions in the gastric mucosa or the acidity of the gastric juice depends on the rate of flow of the juice in the glandular tubules, while the rate of flow in its turn depends on the intensity of the secretory process and the diameter of the glandular lumina.

c) The neutralization, dilution and buffering of HCl by food, non-parietal secretions and extra gastric juices (pancreatic, biliary, saliva, etc.). The functions of many of these substances are not well understood nor have they been thoroughly investigated.

The acidity of the gastric contents rises as a result of the secretion of acid in response to a meal. However, it does not rise excessively, because the stimuli for secretion are withdrawn. If this withdrawal of stimulation does not check the rise of acid concentration, self-regulatory mechanisms such as acid inhibition and entrogastrone becomes effective.

Babkin[20] supports the view that variations in the secretions of the different gastric epithelia which participate in the formation of gastric juice determine the character of the composite secretion. According to Babkin there are four groups of cells present in the gastric mucosa which contribute their secretions to form what is called gastric juice. These are the peptic cells, the parietal cells, the mucus cells of the neck and the surface epithelium cells. The qualitating changes that occur under physiological conditions in gastric secretions as well as in other digestive secretions produced in response to various stimuli by glands of compound structure, may be due to the unequal quantitative activity of the different group of epithelial cells.

VII. INFLUENCE OF THE LIVER ON GASTRIC SECRETION

The liver is strategically located so that all substances absorbed or secreted into the portal system normally must transverse it before entering the general circulation, and thus it plays an important role in the metabolism of many compounds.

Partial hepatectomy in dogs leads to the development of peptic ulcer[171]. Autopsy studies on patients with cirrhosis show an

increased number of duodenal ulcers[122, 61]. The frequency with which an ulcer has been observed after porto-caval shunts varies with the type of shunt, and is higher in those with large shunts.

Numerous mechanisms by which cirrhosis may predispose to ulcer formation have been suggested. Bockus[21] mentioned malnutrition, decreased amounts of bile, central nervous system damage and congestion of gastric mucosa. The experimental results show that portal hypertension and procedures which divert portal blood around the liver increases the gastric secretion which leads to ulceration.

Irvine et al[104] supported the role of histamine, because this is produced normally during digestion of meat by conversion of histidine by intestinal bacteria. He concluded that histamine which is absorbed into the portal blood, is normally destroyed in the liver. This does not occur when the portal blood bypasses the liver in cirrhosis or following the surgical creation of shunts. Clark[28] suggested the possibility that the concentration of ammonium in blood might represent still another factor as it increases the secretion of gastric juice. This effect of ammonium upon gastric secretion is not diminished by vagotomy or by antrectomy. Clark concluded that the action of blood ammonium as a secretagogue is similar to that of gastrin[29].

VIII. THE PATHOLOGIC PHYSIOLOGY OF PEPTIC ULCER

1) Acid - Peptic ulcer is the result of the digestive action of pepsin, but the activity of this enzyme depends upon the acidity of gastric juice[70]. Maximum acidity occurs at about pH 2.0. It has been shown that the mean concentration of acid in the gastric and proximal duodenal contents under basal conditions is higher in patients with duodenal ulcer than in persons without ulcer. This has been determined by duodenal aspiration

technics[114, 179]. The mechanism of hypersecretion of acid in patients with duodenal ulcer is not fully known. The theories which have been advanced are as follows: -

a) Impaired inhibition of secretion. Some patients with marked hypersecretion had normal inhibition by acid and so a defect in this mechanism cannot be the cause of hypersecretion[94].

b) Decreased local resistance. Other investigators consider atrophy of Brunner's glands, which might decrease resistance to acid in duodenal ulcer patients.

c) Excessive secretory stimuli.

d) Increased sensitivity of the glands to stimulation. Cox[30] found that there are an increased number of parietal cells in the duodenal ulcer patient. It is not known why this is so, but it may be a constitutional factor. Another possibility is that prolonged increased stimulation of secretion leads to hyperplasia of the parietal cells. Experimental evidence in animals cited by Cox supports such a hypothesis.

Sircus[203] found that with an increased duration of duodenal ulcer symptoms there occurred an increase in secretory rate.

2) Pepsin - As with acid secretion, patients with duodenal ulcer show increased rates of pepsin secretion. The concentration of pepsinogen in blood serum and its rate of excretion in the urine are also increased in patients with duodenal ulcer. Similarly a decrease in pepsinogen and free acid occurs when patients with duodenal ulcer are treated by vagotomy or gastric resection. It is assumed that variations in pepsinogen levels in blood and urine reflect mainly variation in the gastric secretory capacity of pepsin secretion[6].

3) Mucus - Normally mucus of gastric juice occurs in two forms,

visible and dissolved, and contains two types of mucopolysaccharides[143]. The methods available for measurement of these in aspirated gastric juice have failed to reveal differences between persons with and without ulcer, except to show that an increase in acid secretion and an increase in one class of muco protein are associated[95].

4) Gastroduodenal motility - The frequency and pressure waves during fasting in the stomach and duodenum of patients with duodenal ulcer do not differ from those of a normal subject. Peristalsis may be increased in patients with peptic ulcer who are suffering pain[204]. There is no evidence for the existence of a dearrangement of gastroduodenal motor activity which might act as a causative factor in peptic ulceration.

5) Blood group - Observations from many countries have established the fact that persons who possess blood group O have a higher incidence of peptic ulcer than those of other groups. Another genetic factor which may be involved in the etiology of peptic ulcer is the secretory status[31].

IX. GEOGRAPHICAL AND ENVIRONMENTAL ASPECT OF PEPTIC ULCER

The unequal distribution of peptic ulcer disease all over the world has led many workers to the opinion that geographical and environmental factors are of etiological importance[220]. The results from various parts of the world show that the incidence of ulcer varies widely from place to place and from time to time. The incidence of peptic ulcer depending on the population studied varies from 0.5 - 20% [239].

In both animals and man it has been shown that the volume and acidity of gastric juice is higher in autumn and spring than in the other seasons[134]. Surveys from various parts of the world show a peak incidence in every month of the year except July. In most areas of the world, duodenal ulcers have predominated in clinical studies,

and males have been the chief victims[102]. It is also interesting to know that perforated peptic ulcers have been noted to occur in great numbers during periods of heavy air raids[202].

CHAPTER II

REVIEW OF PREVIOUS METHODS FOR EXPERIMENTAL PRODUCTION OF PEPTIC ULCER

I. INTRODUCTION

Three factors have been implicated in the experimental production of peptic ulcer: -

1) Local mechanical

2) Systemic

3) Secretory

How an ulcer forms, why it becomes chronic and how it heals are still debatable. Prior to Virchow's time experimental studies of the problem of peptic ulcer had not been carried out.

In evaluating the relationship between the effect of a drug reaction and ulceration in man, one must assess not only the pharmacological action of the drug, but also the effect of the disease itself, the possibility of the ulcer being coincidental, and the significance of the person's susceptibility to peptic ulcer formation. The experimental design to investigate the ulcerative effect of the drug in man can be either similar or dissimilar to that in animals. One of the most practical tools in this evaluation in man is the measurement of the output of free hydrochloric acid per unit of time, as well as the viscosity of gastric secretion before, during and after the administration of the drug. The importance of this examination was suggested by Rider and his co-workers[168] who found a decrease of gastric acidity associated with an increase in uropepsin activity as the first evidence of injury to the gastric mucosa by radiation.

From the review of previous literature covering peptic ulcer one receives the impression that great caution must be exercised in

in drawing conclusions from the result of studies based on experimental ulcers. Although acute ulcers can be produced readily in certain animals, the conditions necessary for this are artificial, and alter seriously the normal anatomical and physiological relationship of the organs involved. Usually these alterations are far different from any that could possibly occur in human subjects with peptic ulcer. Species differences, too, constitute a hazard in comparing experimental ulcer in animals with spontaneous ulcer in man.

II. LOCAL FACTORS FOR THE PRODUCTION OF EXPERIMENTAL ULCER

Layne[118], Hanzlik[76], Turck[207], and others used local irritant agents on the surface of the stomach and duodenal mucosa for the production of ulcer. The agents used were hot fluids, "cheap whisky", 20% ethyl alcohol, salicylic acid, mustard oil and curry powder. The superficial ulcers in these experiments were mainly due to coagulation of protein in the cells with generalized hyperemia and gastritis. Dragstedt[32] and Woodward[164] used dilute hydrochloric acid and acid pepsin solution for the production of ulcer. They also studied the protective action of sodium bicarbonate and relative sensitivity of various portions of bowel to the acid peptic mixture.

It is reported that Wittneben and Ritter[102] in 1886 studied the relation of external trauma to ulcer. They struck the animal on the epigastrium with a hammer! Submucosal hemorrhages were noted at the site of injury and they considered hematoma in the submucosa as the starting point of the ulcer.

Irradiation seems to be the method by which one may obtain gastric, duodenal or ileal ulcer which persist for a considerable length of time after the responsible agent is withdrawn. Radium needles and

x-ray produced necrosis of the epithelial tissue and changes in the blood vessels[33]. If the dose was large it produced perforation. Proliferation of these cells led to an over production of connective tissue, resulting in an indurated ulcer.

Colon bacilli, streptococci and mycotic organisms as etiologic organisms have been considered in the production of ulcer. These organisms were given by mouth or by the intravenous route daily for several months to produce acute ulceration. Rosehow[169] believed that the gastric mucosa when digested by acid juice forms an acute ulcer, which becomes chronic from organisms coming from the blood. Pulvertaft[160] attempted to induce chronic ulceration by injecting the organisms into an artificial defect made in gastric and duodenal mucosa, but had no success. Other investigators gave importance to bacteremia and infectious diseases playing a role in the formation of ulcer[137]. Ivy[102] concluded that in order for infection to play a role at least two factors must be contributary.

1) General lowering of bodily resistance

2) Temporary hypoacidity or anacidity

Porell[98] studied the basal secretion in normal dogs following abdominal incision only and with superimposed infection. Gastric acidity was found to be increased in the infected series. He concluded that in the infected group, factors other than stress are important for ulcer production and these factors may be immunologic in nature.

Palmer[162] suggested that a Herpes simplex virus, which become established in the vagus nerve, through a break in the gastro-intestinal mucosa may be responsible for duodenal ulcer in man, but experimentally no virus was obtained from the nerve.

Gastric motor disturbances were produced by interfering

with the normal free movement of the mucosa over the muscularis by injecting irritants. This led to ulceration[102]. The relation of epigastric hernia to incidence of ulcer was studied by Ivy and his associates, but no correlation was found[138]. Ogilvie[156] considers anatomical factors important in relation to preponderance of ulcer on the lesser curvature of stomach. He found that the lesser curvature is fixed and also that the mucosa along the lesser curvature is fixed to the underlying muscularis and is smoother than the mucosa of other portions of the stomach.

Circulatory disturbances. It is reported that Pary[102] was the first to call attention to the blood supply of the stomach in protecting the mucosa from digestion. Ligation of the left gastric artery and vein and partial occlusion of the superior mesenteric vessels produced ulceration of the stomach and duodenum. The effect of subtotal devascularization of the stomach by the Somervell technic was studied on the Mann-Williamson ulcer; such devascularization failed to protect against ulceration[77].

It is reported that Panum[102] in 1862 introduced emboli by injecting silver intravenously and produced necrotic areas in the stomach. Later several substances were used to produce emboli; for example, lead chromate, oil suspension, formalin, charcoal, alcohol, lycopodium, fat, lampblack and glass beads. Payr[102] produced thrombosis in omental vessels by burning and freezing with ethyl alcohol. He concluded that emboli go in a retrograde direction into the submucosa and mucosa of stomach and duodenum and produce ulceration. Children have effective valves which prevent retrograde flow and hence the ulcer is rare in children. Erythrocyte stasis in gastric vessels and abnormal gastric flow due to agglutination

of red cells has been suggested as the cause of acute vascular disturbance underlying peptic ulceration[109]. The relation of venous stasis with ulcer was studied by ligating either the splenic or portal vein[8]. Stasis does not cause ulceration, but only hastens the appearance of ulcer following the injection of histamine. Nicoloi[102] studied the relation of splenomegaly to gastroduodenal ulcer, but came to no conclusion.

The relation of vasomotor disturbances to ulceration was studied by injecting large doses of epinephrine intraperitoneally. This resulted in lesions varying from petechiae to ulceration in all parts of the digestive tract[159]. Epinephrine causes prolonged vasoconstriction, producing a shock-like condition with tissue anoxia, a drop in capillary pressure, increased permiability, edema and finally tissue necrosis. These findings were also observed in shock produced by bleeding the experimental animal, and also by giving toxic doses of Ergotamine[54].

It is reported that Ramond et al studied the lymphatic drainage of the stomach and found the lesser curvature of the stomach devoid of lymphatics. He stressed its importance to explain the ulcer diathesis.

III. GENERAL OR SYSTEMIC FACTORS

a) Burns

Curling in 1842 first noticed gastroduodenal ulceration in extensively burned patients. Other investigators studied the relation of percentage and degree of burn with the incidence of ulcer[99]. Sixty-three percent of patients with third degree and 50 - 60% body surface burns develop ulceration. Various theories were forwarded to explain the production of ulcer after burns.

i) Absorption of toxin from the burned area. This fact is not established[170].

ii) Release of histamine. Animals receiving histamine subjected to burn develop ulcer earlier[148].

iii) Haemoconcentration. Preventing haemoconcentration by administration of plasma reduces the incidence of gastroduodenal ulceration[102].

iv) Excessive gastric acidity due to increased gastric motility[149].

v) Spinal reflex from burned skin. When this reflex was abolished by division of the nerve, no ulcers developed[102].

vi) Irritant action of noxious bile. Bile was considered important in the production of Curling's ulcer, because the ulcers occur in the duodenum in 71% and in the stomach in only 10%[78].

vii) Adrenal insufficiency[102].

viii) Infection. The incidence of ulceration increases with sepsis and is decreased by administering antibiotics[78].

ix) Shock. The most logical explanation of the Curling ulcer seems to be shock, which follows severe burn. Shock leads to congestion of the mucosa, rendering it susceptible to digestion by acid pepsin[9].

b) Drugs used for the production of peptic ulcer are:

1) Histamine. Continuous stimulation of the parietal cells was secured by Code's[25] method of implanting pellets of histamine mixed with beeswax intramuscularily or subcutaneously. Histamine acts directly

on the parietal cells and produces continuous gastric secretion leading to typical chronic perforating ulcers in the stomach or the duodenum. Histamine also increases pancreatic secretion by stimulation of secretin which is stimulated by gastric juice in the intestine[79]. There is no satisfactory evidence of a significant increase in the histamine content of blood in the duodenal ulcer patients[110]. Baronofsky[10] studied the percentage of gastric resection needed to protect against histamine induced ulcer. In man peptic ulcer may occur in susceptible persons treated with repeated histamine injections. Such ulceration has been reported in patients treated with histamine injection for multiple sclerosis[80].

It is evident from the data presented that the ulcerogenic properties of histamine are due to one or more of the factors described. Excessive gastric secretion regardless of the mechanism of its production, predominates in ulcer formation by histamine. It is interesting that vagotomy as well as antrectomy reduce the response of a Heidenhain pouch to histamine[154].

2) Cinchophen. In dogs cinchophen in a daily dose of 200 mg. per kilogram will usually cause peptic ulcer within three weeks. The lesion simulates an erosive gastritis. Healing of the ulcers occurs promptly after discontinuing administration of the drug[199]. Various factors were postulated in the ulcer formation. These are: -

a) disordered motility in the region of the pylorus[103]

b) release of histamine[11]

c) reduction of the protective mucus barrier[199]

d) depression of duodenal secretion and changes in Brunner's glands

e) effect on the detoxifying mechanism of the liver, particularly with glucuronic acid conjugation[12].

3) Phenylbutazone. Prolonged administration of phenylbutazone either orally or parenterally produces gastroduodenal ulceration[11]. A single dose intragastrically produces an increase in gastric acidity. The ulceration is thought to be due to injury to the mucosa resulting in an increased susceptibility to digestion by hydrochloric acid and peptic secretion. The effective ulcerogenic dose is much smaller in man than in animals and ulceration occurs more readily in subjects susceptible to peptic ulcer[13].

4) Caffeine. Orally or parenterally administered, caffeine is a potent stimulant of gastric secretion by direct action upon the parietal cells[172]. The fact that patients with duodenal ulcer have a marked gastric response to caffeine suggests that excessive intake of caffeine may be a contributory factor to ulcer formation[139].

The evidence suggests that the mechanism for ulcer formation related to caffeine is similar to that of histamine, that is the combination of increased gastric secretion and lowered resistance of gastroduodenal mucosa.

5) Salicylates. Schnedrof, Bradley and Ivy[194] observed that prolonged administration of aspirin in normal dogs and in dogs with Heidenhain pouch resulted in an increase of gastric secretion. Ecchymosis, hyperemia and ulceration of the gastric mucosa also has been reported by other workers.

Brown and Mitchell[14] reported that gastric hemorrhage in 70% of patients with duodenal ulcer was related to the use of salicylates for headache or arthritis. These data support the hypothesis that acetylsalicylic acid can produce local gastric mucosal irritation and hyperacidity.

6) Reserpine. Is now widely used in the therapy of hypertension and certain emotional disorders. Its relation to peptic ulcer was

studied by Anderson[1] who observed increased excretion of 17-ketosteroids in three monkeys maintained on reserpine for nine days, but not in the hypophysectomized animals. These findings suggested to him that reserpine can activate the ACTH steroid release mechanism.

The probable factors behind the ulceration by reserpine may be either a direct effect upon the gastric mucosal cells, or an indirect result due to the liberation of histamine or the activation of the ACTH steroid release mechanism, or a combination of these factors.

c) The role of immunization was first studied in 1903. Gastrotoxin was prepared by an extract of gastric mucosa, and injected into dogs. This resulted in hypersecretion leading to hyperemia and ulcer formation[102].

Later it was believed that allergy or anaphylaxis plays an important part in the etiology of ulcer formation. It was believed that a break in the mucosa with the introduction of heterogenous protein might produce vascular disturbances leading to ulcer. The same phenomenon occurring in skin is called "Arthus Phenomenon". Here healing is complete, whereas in the stomach it does not heal because of the constant corrosive action of gastric juice. Similar results were obtained by other experimentors by using a local injection of protein into the gastric mucosa. Other groups believe that bacteria may act as foreign protein or that ulceration might be due to sensitivity to split product of animal protein. None of the ulcers produced by this method become chronic[102]. The possibility now remains that such a factor may be responsible in human peptic ulcer.

d) The role of nutritional disturbance in the etiology of peptic ulcer was studied by feeding the animal a diet rich in spices for a long time. This produced degeneration of Meissner's and Auerback's plexus, but without production of ulcer[21]. Similar findings were obtained in resected

stomach specimens from ulcer patients in South India where the diet is rich in spices.

Dogs dying of starvation often show multiple erosions and ulcerations. From evaluation of previous experimental work it is difficult to find a specific deficiency of importance for ulceration in dogs or in humans. Most of the work on nutritional deficiency was done on rats and interpretation of results is difficult because of species differences, and also because of anatomical and physiological variations in the gastro-intestinal tract.

It was believed that Vitamin A deficiency leads to abnormal epithelium, which is unable to resist acid pepsin and hence leads to ulceration[102]. It is also reported that deficiency of factor II in Vitamin B (chick anti-dermatitis factor) and pellagra producing diets produce ulceration[20]. The cause of this ulceration might be due to fatty changes in the liver. Vitamin C and calcium deficiency are reported to cause ulceration in the gastrointestinal tract in small animals, but not in the dog. In dogs Vitamin C given in large doses has a prophylactic effect against cinchophen ulcer. Severe protein deficiency in dogs can result in a high incidence of peptic ulceration. Protein deficiency or nutritional deficiency interferes with the maintenance of body tissue and may predispose to ulceration of gastrointestinal mucosa. With vitamin deficiency, no change was seen in histamine stimulated gastric secretion.

IV. ENDOCRINE DISTURBANCES

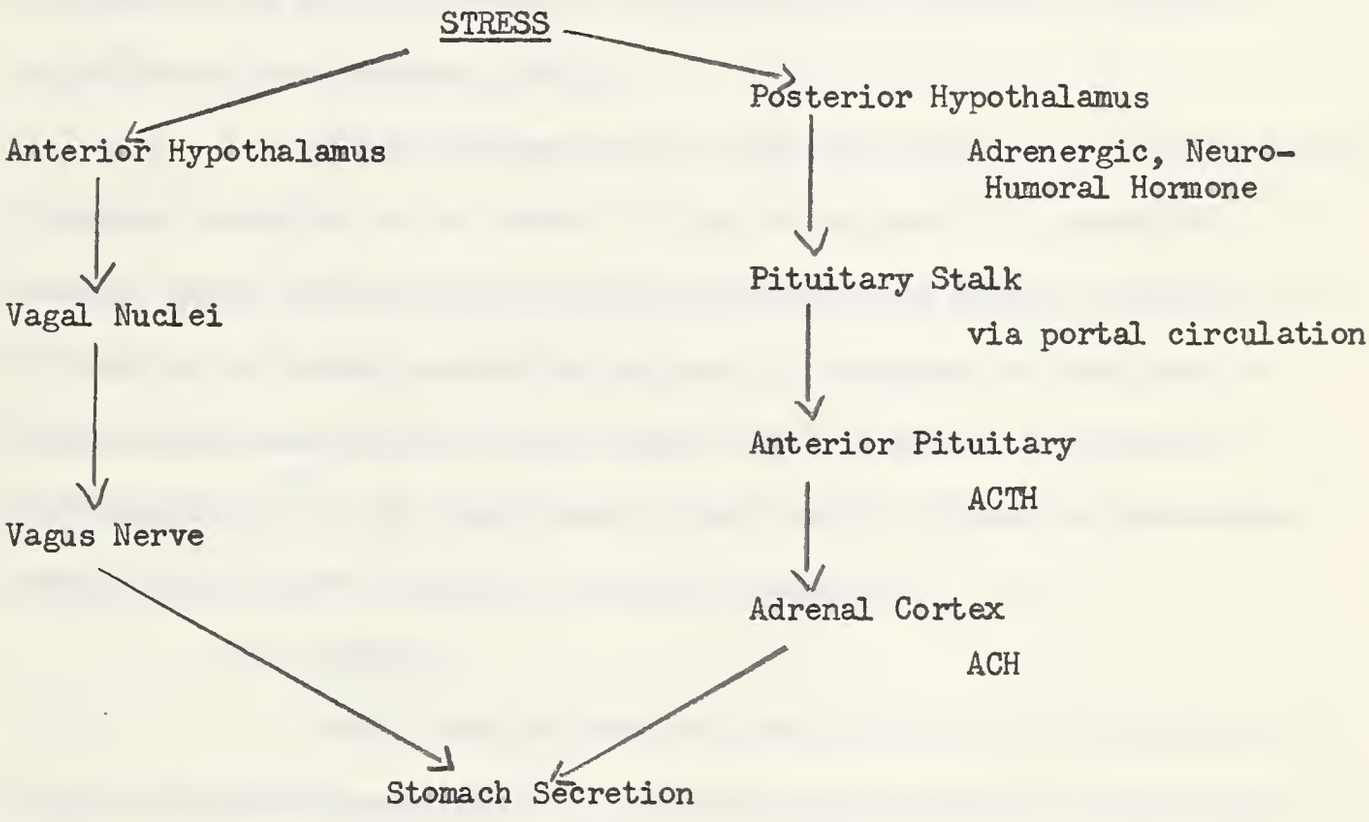
a) Adrenals

Adrenalectomy in dogs lead to gastric or duodenal ulceration and in the dog with duodenal ulcer leads to perforation[221]. Mann-Williamson dogs treated with cortisone lived longer than the controls. With ACTH they

* * *

also lived longer, but ACTH was not as effective as cortisone[195]. The stimulating effect of cortisone is exerted directly on gastric glands[243]. Since vagotomy abolishes the hypersecretion, it is evident that hypersecretion is produced by excessive secretory impulses over the vagus nerves and is not due to the liberation of cortisone from the adrenal gland as a part of the so-called stress phenomenon. The pathways by which the effect of stress may be relayed from the hypothalamus to the stomach are considered to be neurogenic[161] and hormonal[65]. These pathways are shown in Figure 3.

FIGURE 3



Cushing Ulcer

Curling Ulcer

Physical or emotional stress is thought to activate the posterior hypothalamus with a resulting increased output of corticotrophin by the anterior pituitary gland. Corticotrophin acts upon the adrenal cortex, releasing steroid hormones, stimulating the gastric glands to secrete acid and pepsin[110].

An increase in gastric hydrochloric acid, pepsin and chloride has been demonstrated in intact and pouch dogs, also in vagally denervated and antrectomized dogs following intramuscular injections of ACTH[213].

In man, corticotrophic hormone must be administered in large doses (100 - 160 units daily) for 3 to 4 weeks or larger to produce a significant elevation in the output of hydrochloric acid and pepsin[108]. Whether steroids form new ulcers or whether old ulcers are reactivated by the administration of steroids cannot be evaluated, unless consideration is given to the dose, duration of therapy and the effect of previous medication with ulcerogenic drugs.

The mechanism of ulcer production during the administration of adrenal steroids is not clear. It may be related to a combination of factors, among which are increased gastric acid and pepsin secretion, a decrease in the mucus protective barrier or resistance of the gastric mucosa, interference with tissue repair and/or vascular or metabolic dearrangements[173]. The importance of acid peptic factors is emphasized because these ulcers respond to antacid treatment.

b) Thyroid

Total thyroidectomy did not influence the development of ulcer in Mann-Williamson dogs[82]. Feeding excessive doses of dessicated thyroid depressed the rate of secretion and concentration of acidity in gastric juice during the first hour of feeding. Observation in thyrotoxic patients show a significant increase in incidence of achlorhydria and delay in gastric emptying. Friedman[55] carried out a complex series of experiments with the adrenal, thyroid and parathyroid glands in relation to the etiology of ulcer. He concluded that gastric lesion might be

dependent upon adrenal insufficiency as well as excess of thyroid gland. Duodenal lesion on the contrary depends upon thyroid hypofunction as well as upon excess of adrenalin. Gastric and duodenal lesions might be dependent upon the alternating effect of hypo and hyper function of the adrenals.

c) Lesions in the hypothalamus or removal of the posterior pituitary in dogs produce increased gastric motility, spasticity, erosion and acute ulceration of the gastroduodenal mucosa[102]. Confirmation of previous results were done by other investigators by giving large doses of posterior lobe extract with production of lesions in the stomach. Vandenberg et al[196] indicated that hypophysectomy in dogs reduces gastric secretion by 50%. The role of the hypothalamus in relation to stress has been discussed under the adrenals.

d) Relation of peptic ulcer with primary hyperparathyroidism

The chronic duodenal ulcer seen in clinical hyperparathyroidism in man has not been reproduced in experimental animals by the administration of parathyroid hormone, intravenous calcium salt, or Vitamin D. Large doses of parathyroid extract do, however, produce hyperemia, hemorrhages and necrosis of fundic glands within the stomach of dogs and rats[15].

These workers concluded that parathyroid hormone influences gastric secretion by hypercalcemic inhibition of vagal activity[197], and also alters gastrointestinal motility, secondary to hypercalcemia[74]. Calcinosis of the gastric wall, liquefaction of gastric mucus and the destruction of the ground substance of the mucosa has also been suggested, but there is no evidence that it produces peptic ulcer in patients with chronic hyper-

parathyroidism[67]. Clinical studies with peptic ulcer proved by roentgenogram surgery or autopsy was demonstrated in 9.1% in one series of patients with primary hyperparathyroidism[157]. Although primary hyperparathyroidism was twice as common among females, peptic ulcer in hyperparathyroidism was observed more frequently in men (14.9%) than women (6.2%). Peptic ulcer may not be directly related to hyperparathyroidism since:

a) The symptoms of ulcer and hyperparathyroidism did not seem to coincide with each other in severity.

b) The peptic ulcer generally precedes the onset of clinical hyperparathyroidism.

c) The ulcers often persist or become worse after removal of the parathyroid adenoma. The clinical and experimental data revealed that gastric secretion is not apparently increased in hyperparathyroidism.

e) Endocrine tumours and peptic ulcer

Parathyroid adenoma - The parathyroid adenomas were the first endocrine gland tumours whose hyperfunction was associated with a significantly increased incidence of peptic ulceration. Mann[102] reported an interesting coincidence in a dog having carcinoma of the thyroid and chronic duodenal ulcer. He attributed this to parathyroid deficiency. Rogers[175] in 1946 called attention to the marked similarity between the gastrointestinal symptoms in hyperparathyroidism and peptic ulcer. The overall incidence of peptic ulcers associated with parathyroid tumours proved to be about 13% and these usually occurred in the duodenum[140]. Gastric hyperfunction has not been found associated with parathyroid tumours.

2) Adrenal Tumours - Over activity of the adrenal cortex has long been suspected of playing a role in the etiology of ulcer. There is little evidence linking any type of adrenal tumour with an increased incidence of peptic ulceration. Peptic ulcer has been reported in 1% of patients with Cushing's syndrome secondary to hyperfunctioning tumours of the adrenal cortex[111]. With adrenal medullary tumours the incidence being estimated at less than 1%[141].

3) Pituitary Tumours - The pituitary glands have little direct effect on gastric acid secretion, and peptic ulceration. Wilson et al[223] found the incidence of ulcer to be 1% in a review of 512 patients with acromegaly.

4) Pancreas - Ellison and Zollinger[244] in 1956 and MacKenzie[147] in 1958 reported the association of an islet cell tumour of the pancreas with recurrent stomal ulceration. They believe that in their cases the hyperglycemic-glycogenolytic factor of the pancreas (glucogen) may have been the factor stimulating the gastric secretion to abnormal levels. This hypothesis has not been borne out, since both human and animal experiments clearly show that glucogen depresses both gastric secretion and motility[174]. The ulcerogenic stimulus is indeed a powerful one, but its mode of action is unknown. Recently experiments have been carried out on this hormone. Serotonin was thought to be a possible etiologic agent because microscopically many of the tumours resembled carcinoid tumours. However, serotonin has been ineffective in stimulating gastric secretion, and the breakdown products of serotonin in urine have not been found to be increased in this disease[83].

Extraction procedures on tumour removed at operation by Gregory and associates[68] have yielded a substance similar to, but thirty

times more potent than gastrin. Half of these tumours are malignant, 20% are aberrant, 10% are diffusely distributed throughout the pancreas and 20% occur in association with additional endocrine tumours.

Histochemical staining of the gastric mucosa in patients with ulcerogenic tumours shows hyperplastic transformation of the gastric glands, and also an increase in the number of parietal cells[242]. These changes are known to occur in experimental animals under prolonged stimulation by histamine[198]. Increased parietal cell mass due to non beta islet tumours probably accounts for the ulcerogenic effect in some of these patients.

The coexistence of ulcer and beta cell insulinomas of the pancreas is rare. There are only two reported cases[242].

5) Polyglandular Adenoma - The polyglandular syndrome has been known for years, but Wermer[222] first called attention to the frequency of associated peptic ulceration of the upper gastrointestinal tract. This incidence has proved to be approximately 40%. The incidence is more common in the patients with hyperparathyroidism in whom peptic ulcer developed, than in the group as a whole. These polyglandular cases support the thesis that the pancreatic non beta islet cell tumours play the dominant role in the etiology of associated intractable ulcer.

f) Sex Hormone

Pregnancy has a beneficial effect on the peptic ulcer, but neither pregnancy nor estrogens had any preventive effect on ulcer produced by cinchophen or histamine on dogs[102]. Clinical observations prove pregnancy and stilbestrol has a beneficial effect on peptic ulceration and ulcer disease in women is not as virulent as it is in the males.

Variation in the secretory activity of gastric pouches occur during various phases of the sexual cycle in female dogs. The significance of these very important observations on the relation of the sex hormone to peptic ulcer is not yet clear. Investigation of pregnant urine led to the discovery of a gastric inhibitory substance. Mann-Williamson dogs treated with extract of pregnant urine lived longer than control[195]. Beal[24] and recently Dragstedt[6] have shown that hydrochloric acid secretion in dogs increases ten times during lactation, which is normal before and during pregnancy in dogs. The possible relationship of the marked rise of blood histaminase during pregnancy to ulceration deserves attention.

CHAPTER III

PRODUCTION OF EXPERIMENTAL PEPTIC ULCER BY SURGICAL METHODS

A) Gastroenterostomy (Fig. 4a)

It is reported that Watt[102] in 1903, while studying the effect of gastroenterostomy in dogs, lost one of his animals with a perforated jejunal ulcer. This important observation led other investigators to study the relation of gastroenterostomy to jejunal ulcer.

Eiselsberg in 1895 produced 25% jejunal ulcers after performing gastroenterostomy with exclusion of the pylorus. It is now a well established fact that the antrum when bathed with alkaline juice stimulates gastric secretion. Dott and Lim[34] suggested antrectomy and gastrojejunostomy as a method of producing ulcer. Devine's modification of exclusion of the pylorus and antrum produce ulcer consistantly in dogs. It is believed that ulcers after gastroenterostomy are due to pouring of alkaline duodenal juice in the stomach, which is a powerful stimulant of gastrin mechanism. Antrectomy subsequent to gastroenterostomy resulted in a profound reduction in the response to alcohol[224]. The incidence of ulcer in relation to food and distance from the pylorus of the small bowel used in the anastomosis were studied, and it was found that the incidence of ulceration increased as the anastomosis was moved distally[123]. There was no ulcer after gastroduodenostomy, whereas 100% ulcer developed in one week after gastroileostomy. Alverez[4] noticed that ulcers are usually in the distal loop, which is not bathed completely with juice and food. He modified the gastroenterostomy by anastomosing separately the proximal loop just distal to gastrojejunostomy anastomoses and had only 25% ulcer formation.

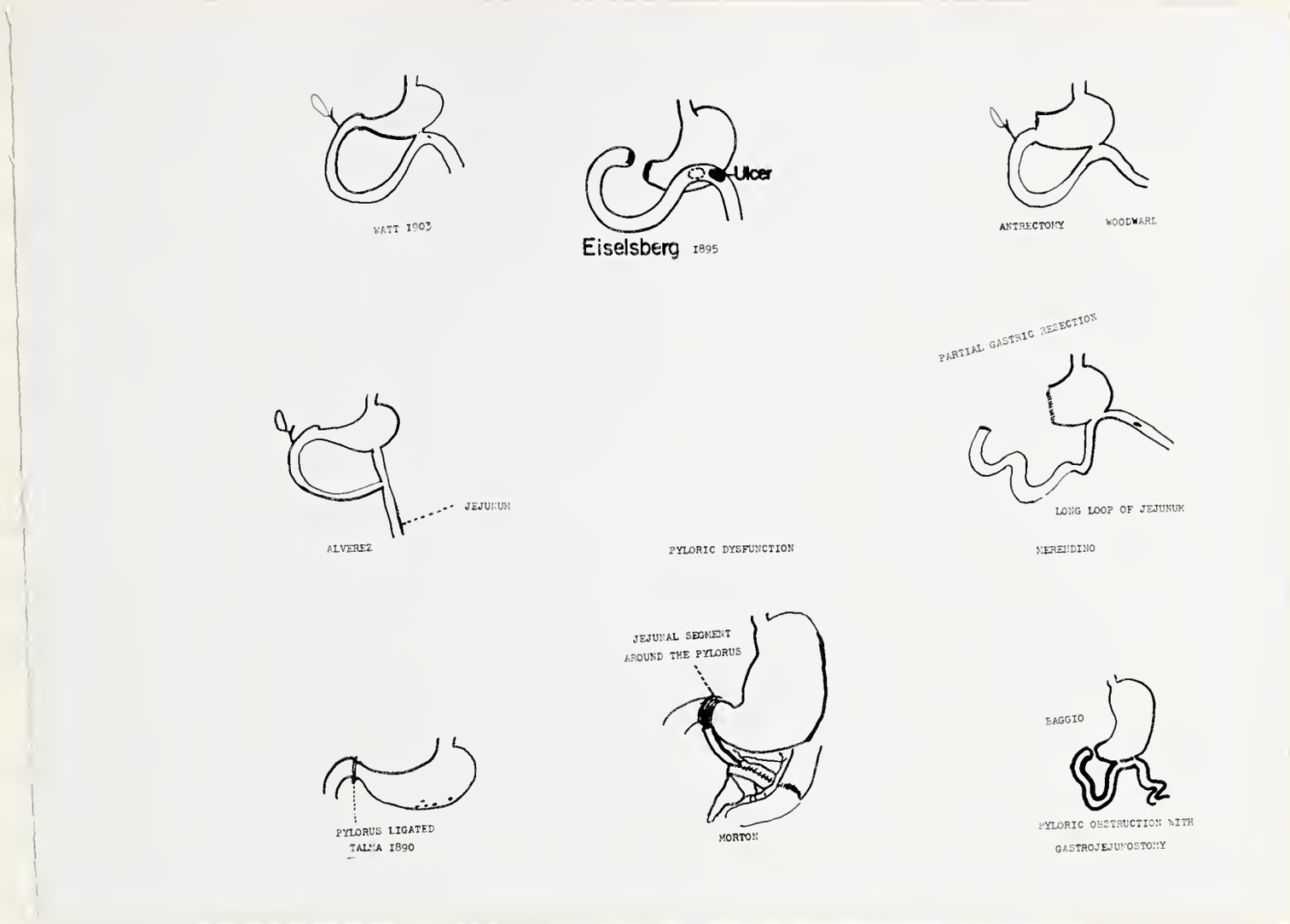
Day and Webster[35] demonstrated that the presence of acid chyme in the duodenum is an important factor in the autoregulation of gastric secretion. The inhibitory effect is lost when acid chyme is deviated away from the duodenum by means of gastrojejunostomy. Merendino[142] demonstrated that gastroenterostomy even with extensive gastric resection is followed by a high percentage of gastrojejunal ulcer if the jejunal loop is long, but ulceration does not occur with short loop anastomosis even after histamine in beeswax was administered.

B) Interference with Pyloric Function (Fig. 4a) in relation to peptic ulcer has been reported to be first studied by Talma[102] in 1890. He ligated the duodenum just distal to the pylorus. Focal hemorrhage and perforation of the stomach occurred. He considered distention of the stomach as an initiating factor. Similarly Baggio[102] obtained a high percentage of ulceration in dogs by gastroenterostomy and with interruption of the pylorus. Morton[124] produced dysfunction of the pylorus similar to pylorospasm by placing a ring of jejunum around the sphincter and developed an ulcer of the duodenum. He considered rapid emptying and loss of balance between stomach and duodenal juices are important in causation of ulcer. Friedman and Hamburger[55] studied the effect of pyloric obstruction on acute ulcer in dogs and concluded that three factors are essential for chronicity of ulcers.

1. Local destruction of mucosa.
2. Active gastric juices.
3. Hyperperistalsis.

They concluded that pyloric insufficiency might be the cause of ulcer by the digestive action of trypsin regurgitation into the stomach and considered the ulcer of the upper gastrointestinal tract to be tryptic rather than peptic.

FIGURE 4a



Gastroenterostomy and pyloric dysfunction

C) The Importance of Biliary and Pancreatic Drainage (Fig. 4b)

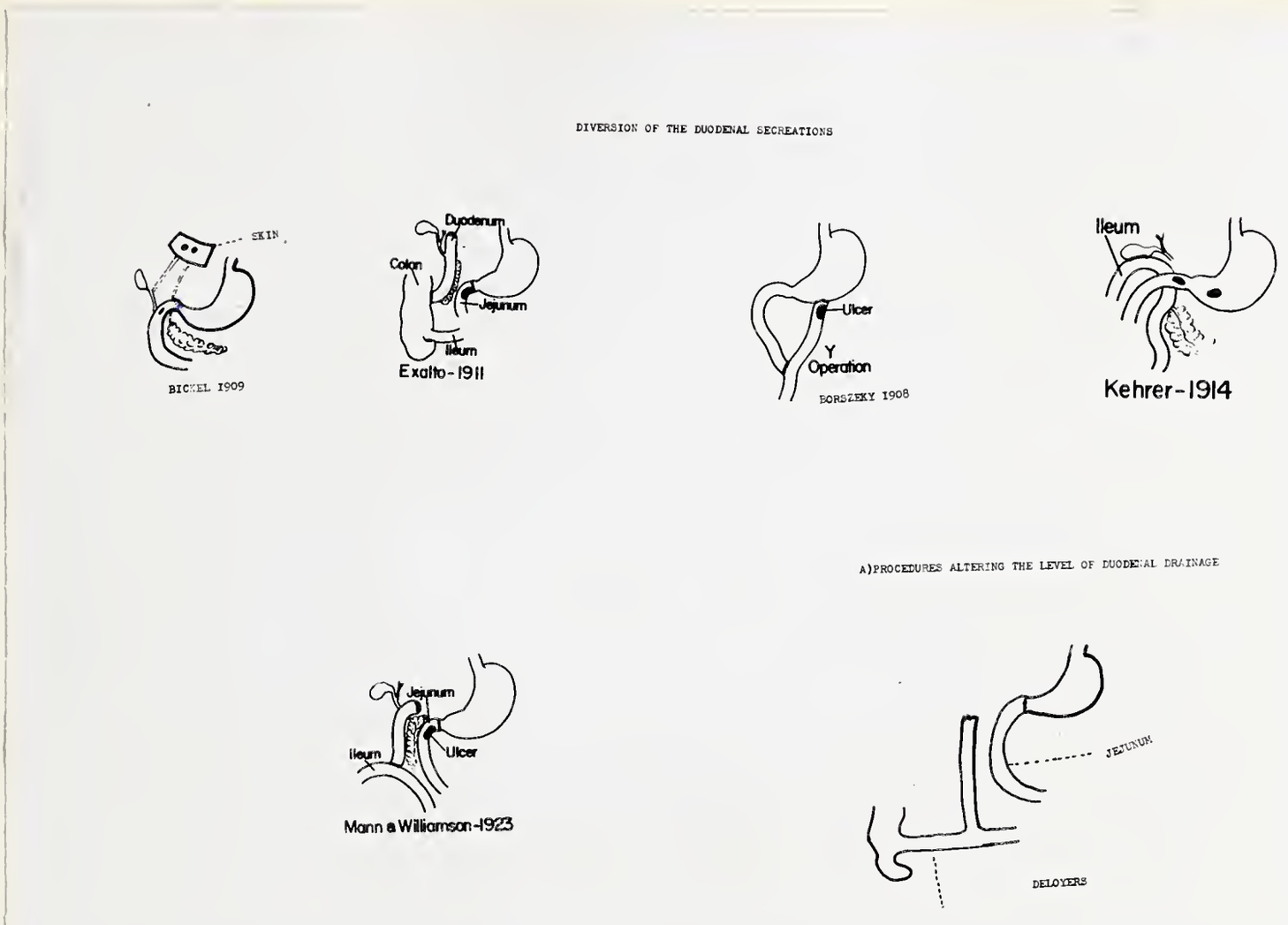
in relation to peptic ulcer was reported to have been first recognized by Bickel[102] in 1909. His operation consisted of closing the pylorus, gastroenterostomy and then bringing the biliary and pancreatic duct out to the skin. The ulcer formed in the upper part of the jejunum and one animal died of perforation. Exalto first produced ulcer with internal drainage. He drained the duodenal secretion into the colon after gastro-jejunostomy. All dogs developed jejunal ulcer. He introduced the etiologic concept of acidity, mechanical trauma and mucosal susceptibility. Borszeky in 1908 produced perforating jejunal ulcer in a dog operated on with an X-type gastroenterostomy. In 1914 Kehrer ligated the common duct and anastomosed the gall bladder and pancreatic duct to the appendix or ileum. Inanition and ulcerative lesion developed in the stomach and duodenum. The dogs survived from 9 to 159 days.

Mann and Williamson[125] in 1923 were the first to produce chronic ulcer, which was reported to have been unsuccessfully attempted by Denk[102] in 1921. The operative steps in the Mann-Williamson procedure are as follows: -

1) Transection at pylorus and closure of duodenal end.
2) End to end gastrojejunostomy utilizing the upper part of the jejunum.
3) Jejuno-ileostomy at 25 cm. above the caecum.

A study of the Mann-Williamson ulcer was done with the help of a properly constructed and well placed non-leaking valve. The gastrojejunal area where the ulcers develop can be brought under endoscopic observation[163].

FIGURE 4b



Diversion of the duodenal secretions and procedures altering the level of duodenal drainage.

Peptic ulcer developed in 100% of operated dogs with the Mann-Williamson procedure. The animal often died of nutritional complications before they lived long enough to develop ulcer. In order to improve nutritional condition of the dog in the Mann-Williamson procedure and also to consider various etiological factors for ulceration, various modifications of this procedure were devised. The procedures done to prove whether nutrition and loss of weight were the main factors concerned in the development of the ulcer can be classified as follows: -

1) Procedures altering the level of duodenal drainage.
2) Procedures to produce nutritional disturbances without internal drainage.
3) Procedures which made it possible to find the specific nutritional deficiency factor.

1) Procedures altering the level of duodenal drainage (Fig. 4b)

It is reported that Deloyers[102] who anastomosed the duodenum to the intestine in dogs approximately 80 - 100 cm. proximal to the caecum developed 50% ulcer. Jenkins[106], Gallagher and Palmer[69] altered the level of duodenal drainage by anastomosing at various segments of the bowel and checked the incidence of ulceration. The above mentioned experimentors conclude that malnutrition and the level of drainage does not alter the incidence of ulceration in dogs. Singer and Sporn[200] considered altered protein digestion in addition to decreased absorbing surface is probably a significant factor in the etiology of the Mann-Williamson ulcer.

2) Procedures to produce nutritional disturbances without internal drainage (Fig. 4c)

McMaster[126] sectioned the first part of the jejunum. The proximal end was anastomosed to the colon and the distal end was closed.

Prepyloric and duodenal ulcer developed. It is reported that Deloyers[102] anastomosed the jejunum to ileum instead of colon. Malnutrition was similar as in the Mann-Williamson dogs. It was concluded that the intestines play some role in causation of ulcer. Edward B. Keefer[116] and associates, from their experiments, conclude that a definite length of terminal ileum is required for the reabsorption of ulcer inhibitory substance and that biliary secretion did not influence ulcer production a great deal.

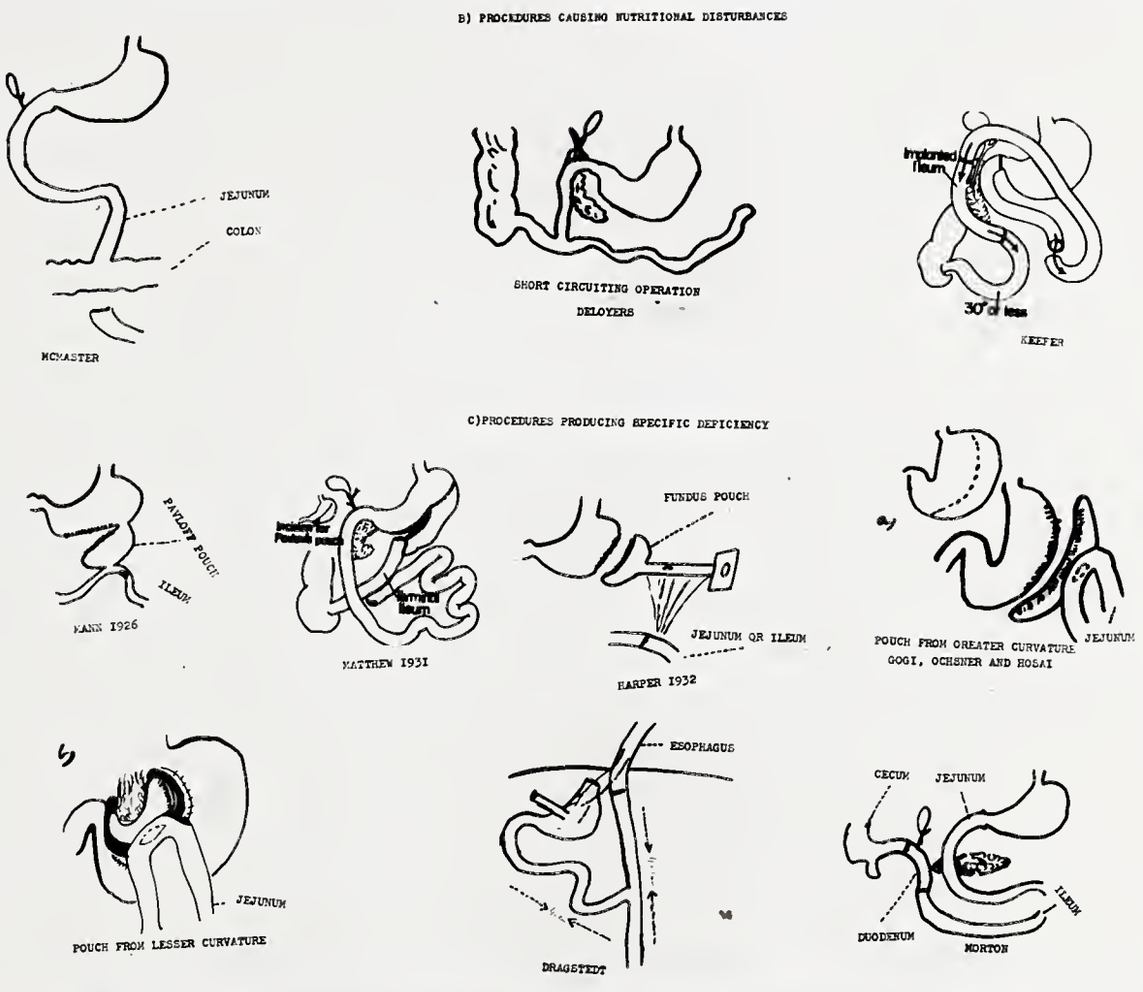
3) Procedures to find specific deficiency factor (Fig. 4c)

In order to find a specific deficiency factor in the causation of the Mann-Williamson ulcer various substances were given to the animal by different routes. Orndorff and Ivy[150] feed the Mann-Williamson dogs with ground pancreas, liver, amino acid, others use histidine and found that it delayed ulcer formation[56]. Since the digestion of protein is rendered impossible by this method, it was considered that an amino acid may be the causal factor.

It has been stated by investigators that ulcers which follow the diversion of the biliary and pancreatic secretion are primarily due to the corrosive action of undiluted gastric juice on the intestinal mucosa.

Mann[146] in 1926 produced experimental Meckel's diverticula by anastomosing Pavlov pouches to various portions of the bowel and produced ulceration. Other investigators led to support the hypothesis that the development of peptic ulcer in a heterotopic gastric mucosa of the Meckel's diverticula depends on biological, chemical and possibly nervous or humoral factors[225]. Matthew[127] using the technic of Mann produced chronic ileal ulcer in 30 - 80 days. In his preparation he kept the pouch free

FIGURE 4c



Procedures causing nutritional and specific deficiencies.

from food material. Wu and Thompson[225] had similar results with a fundic pouch, drained outside with the segment of ileum. Typical chronic peptic ulcer occurred in the loop of ileum draining the pouch. Harper[84] in 1932 used the jejunum in an isoperistaltic manner instead of the ileum and had similar results. These experimentors conclude that in their preparation three factors were responsible for the production of ulcer.

1) Mechanical (stagnation of gastric juice)
2) Chemical (acidity of gastric juice)
3) Mucosal susceptibility of ileum or jejunum.

Other investigators found that ulcer developed in 100% of ileal loops draining the greater curvature, 71% draining the lesser curvature, and none developed ulceration when the cardia was used[70]. By anastomosing the gastric pouch to the transverse colon, with its one end brought out to the skin for proctoscopic examination, the stages of ulceration and the factors responsible for it were studied[228].

Dragstedt[129] observed that ulcers occur in vagally innervated pouches of the entire stomach, and even in the Pavlov pouch which is so constructed as to interfere with free drainage of the gastric secretion. Dragstedt concluded that gastric juice per se is capable of producing ulcer. Other groups of experimentors use the entire stomach pouch with a cannula attached to it. Gastrointestinal continuity was established by anastomosing the esophagus to the jejunum using 40 cm. length from jejuno-jejunal anastomosis. Stomach retained its sympathetic, parasympathetic and vascular connections. Duodenal ulcers occurred in 5 - 8 days. They concluded that continuous secretion of acid and pepsin with hypermotility in empty and fasting stomachs are the factors responsible in ulcer

production[227]. Recently Morton and his associates[128] produced peptic ulceration without an increase in the secretion of acid. In Morton's experiment he transplanted the duodenum to the terminal portion of the small intestine and found similarity in acid secretion of the Heidenhain pouch with the duodenum transplanted to the mid-portion of small intestine. He suggested that some factor other than acid is responsible for peptic ulceration in his preparation.

Most of the experimentors agree that the gastric juice is an essential factor for the production of the peptic ulcer. Further experiments were carried out on Mann-Williamson dogs or on other ulcer producing procedures after altering the gastric juice in order to prevent the lesion. The series of experimental procedures done in this connection can be divided in the following two groups: -

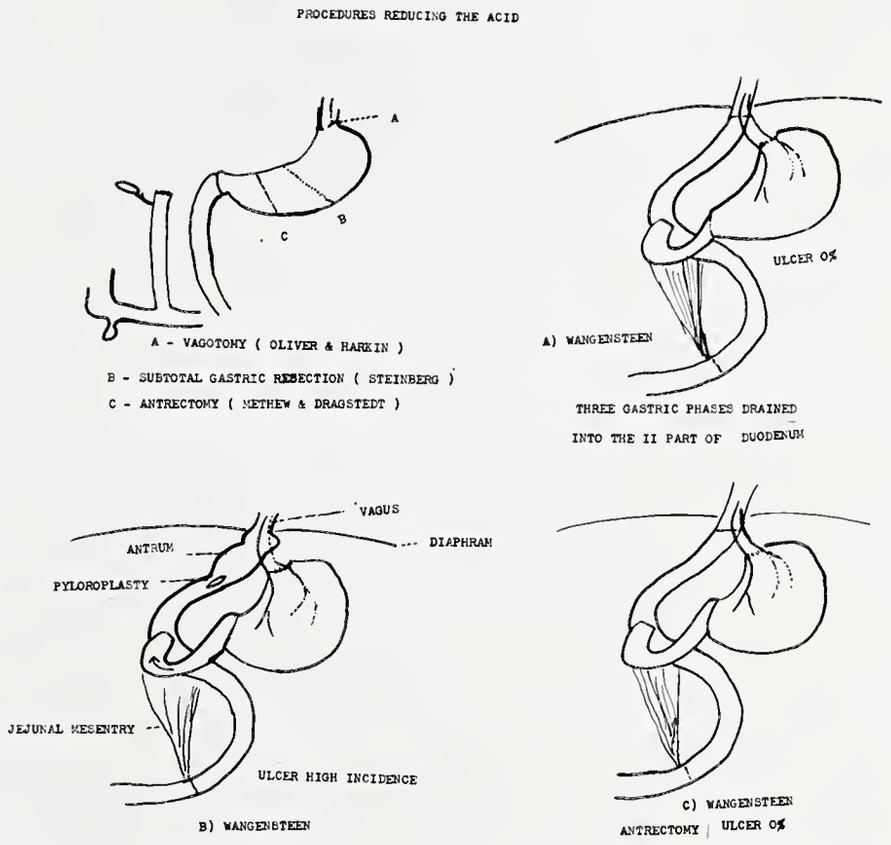
(i) Procedures eliminating or reducing the acid

(ii) Procedures altering the composition of gastric content by intermingling with duodenal secretions.

(i) Procedures eliminating or reducing the acid (Fig. 4d)

It is reported that ligation of vessels at the lesser curvature, resection of fundus, and subtotal gastric resection reduces the incidence of ulcer. The incidence dropped from 100 to 10% in Mann-Williamson dogs with subtotal gastric resection[201]. In fundusectomized animals the average volume of gastric contents 4 hours after a meal was about half of the control Mann-Williamson dogs[58]. Matthew and Dragstedt[129] had no reduction of ulcer incidence with antrectomy. Oliver[151] had no beneficial effect with vagotomy in Mann-Williamson dogs, whereas Harkins[85] reported complete protection with vagotomy. Other experimentors conclude that vagotomy protects one-third of Mann-Williamson dogs from stomal ulcer. Antrectomy alone gives two-thirds protection, vagotomy and antrectomy

FIGURE 4d



Procedures reducing the acid.

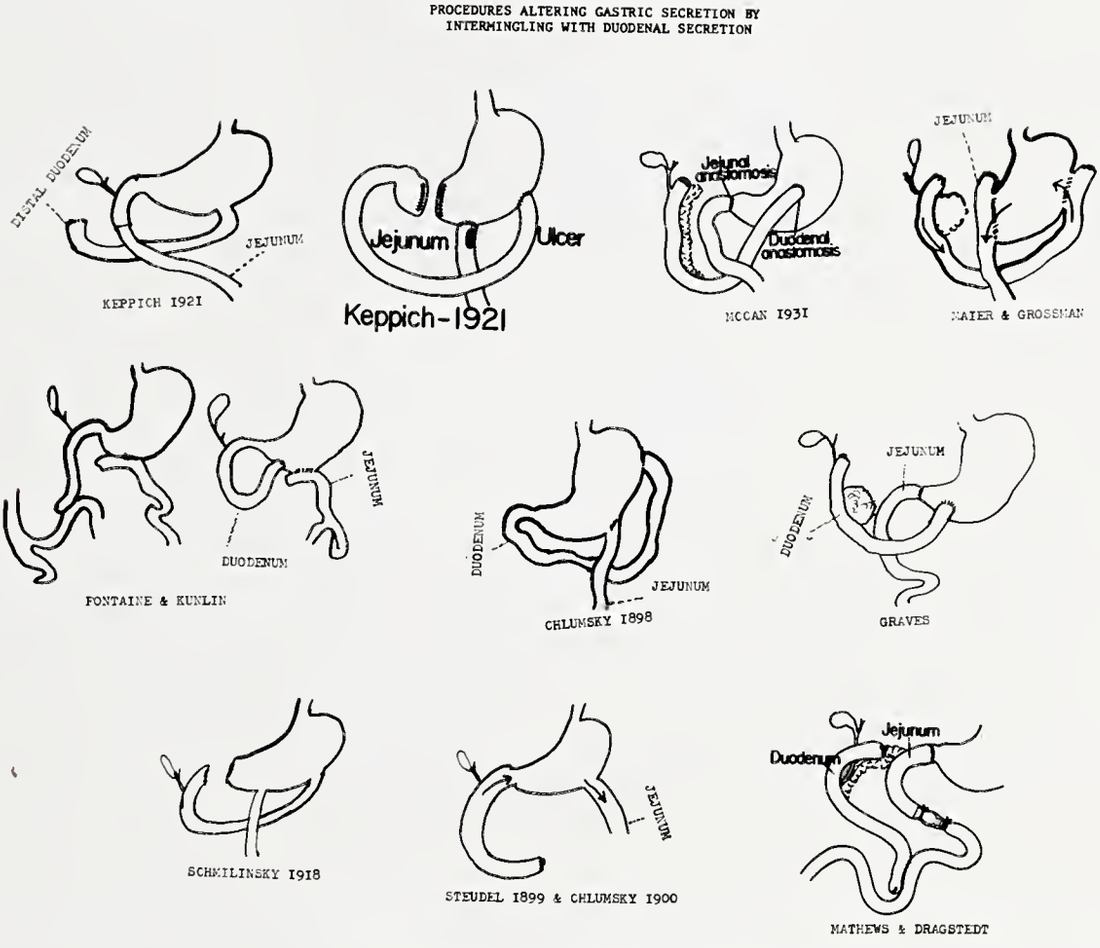
combined was found to be more effective than either procedures[180].

Results with preparations of total stomach pouch with study of gastric secretion of three phases drained by an isoperistaltic jejunal fistula into the second portion of duodenum show similar results of ulcer incidence as in a Mann-Williamson dog[181, 183]. Wangensteen and his associates[228] studied the effect of vagotomy on similar total stomach pouch preparation. In this experiment the stomach was attached to the second part of the duodenum directly instead of a jejunal fistula. Wangensteen concluded that when the antrum was separated from acid secreting portion of the stomach the incidence of gastrojejunal ulcer was higher, and when the antrum remained in contact with acid secreting portion of the stomach gastrojejunal ulcer was rare. These observations give support to the concept of an autoregulatory mechanism in the antral phase of gastric secretion involving inhibition of the antral humoral mechanism by gastric acidity[229]. In Mann-Williamson dogs frequent duodenal feeding by way of antral cannula failed to protect ulcer[182]. This probably was due to the use of the antrum for fistulation.

(ii) Procedures altering the composition of gastric content by intermingling with duodenal secretion (Fig. 4e)

It is reported that Keppich[102] in 1921 divided the duodenum distal to the entrance of bile and pancreatic duct and anastomosed the distal part to the stomach. No ulcer developed. He concluded that the mixture of pylorus and duodenal secretionsare more likely to produce jejunal ulcer than are the duodenal secretions alone. In another series Keppich 4 isolated a segment consisting of pyloric antrum and duodenum - anastomosed to the stomach near the cardia of a gastroenterectomized stomach. All dogs developed deep jejunal ulcer. These results he concluded are due to the effect of antral exclusion. McCann[130] drained the duodenal contents into the fundus of the stomach, jejunal ulcers occurred in 80% of the

FIGURE 4e



Procedures altering the composition of gastric content by intermingling with duodenal secretion

animals. He also, with the fractional gastric analysis, showed that his procedure does not modify gastric acidity. Wangensteen[228] with the same McCann procedure drained half of the duodenal contents into fundus and in the other half of animals he drained into the antrum and produced no ulcer. He concluded that it was not due to the site of drainage. Merendino[142] used the McCann procedure except he used the lower segment of jejunum for gastrojejunal anastomosis. All of his dogs died of spontaneous perforation of gastrojejunal ulcers. Wangensteen attributed the low incidence of ulcer when a high segment of jejunum was used to rich secretin supply of the proximal intestine. Maier and Grossman[132] further reduced the incidence of ulceration by adding partial gastrectomy to the McCann preparation.

It is reported that some experimentors consider that regurgitation of duodenal secretions is important in the role of jejunal ulcers. In their experiments when duodenal secretions were drained directly into the stomach the incidence of ulceration was higher than in those drained into the terminal ileum. Chlumsky[4] in 1898 drained duodenal secretions into the stomach, but all dogs died before any conclusions were reached. Graves[71] drained duodenal content into the antrum and produced no ulcers in dogs. Schmilinsky[4] in 1918 used the same procedure which he originally devised to prevent ulcer. Steudel[4] in 1899 and Chlumsky in 1900 closed the distal end of the duodenum and anastomosed the jejunum to the stomach, thus draining the duodenal secretions backward into the stomach. All animals died before any conclusions were made. Matthews and Dragstedt[129] drained the duodenal contents into the jejunum just distal to gastrojejunostomy and placed a valve in the jejunum proximal to the site of drainage to prevent the regurgitation of biliary and pancreatic secretions. Gastric acidity was not affected, but

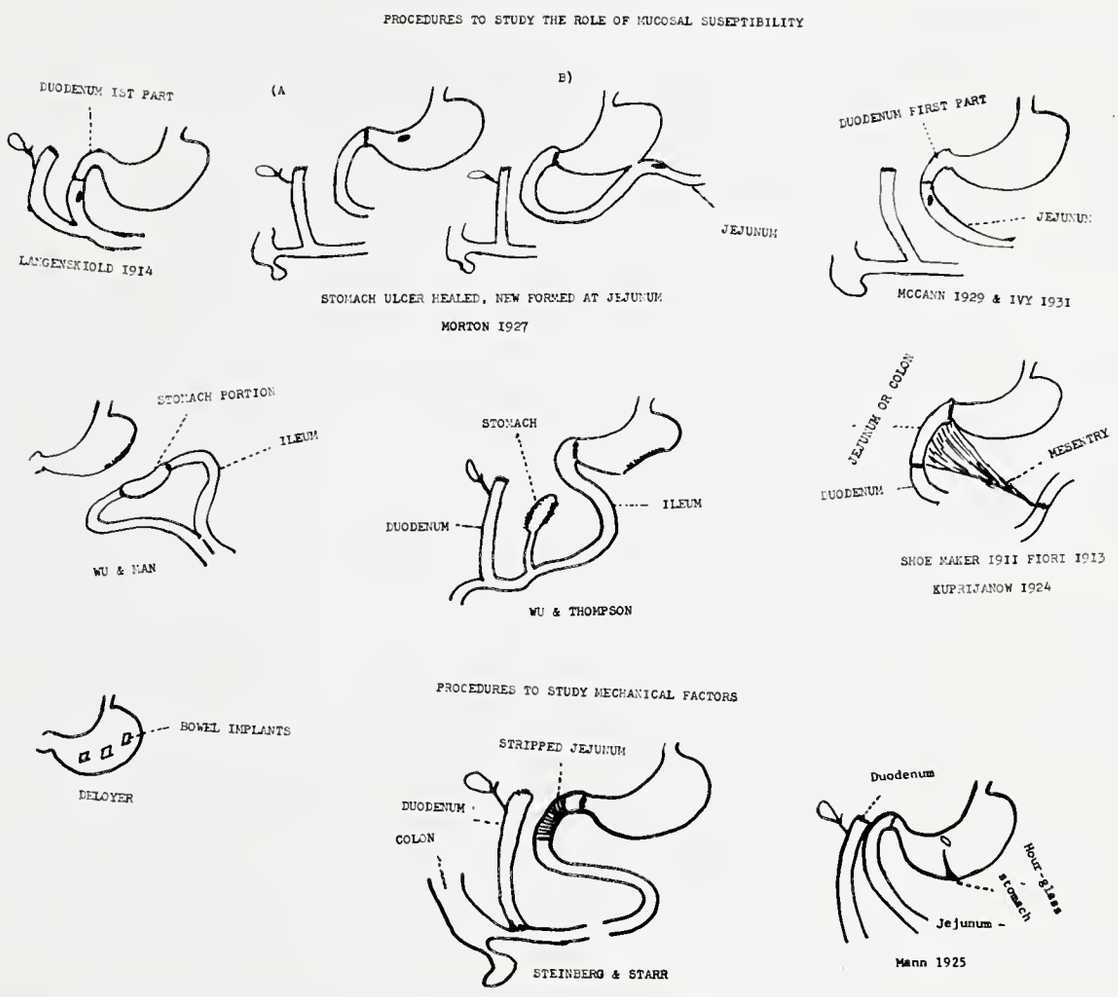
6 out of 10 developed ulcer. Other experimentors anastomose still shorter distances below gastrojejunostomy and find rarer ulcer formation[69]. Mann and Morton[131] (Fig. 4f) first noticed that if a new anastomosis is made distally in Mann-Williamson dogs the original ulcer heals and a new one forms at the site of new gastrojejunostomy stoma.

D) The role of mucosal susceptibility in the etiology of peptic ulceration (Fig. 4f)

It is reported that Langenskiold[4] in 1914 found that the digestive power of gastric juice is lost after it has gone 4 cm. from the stomach and that the acidity is not entirely lost even after 2 - 3 hours of contact with duodenal mucosa. In his experiment he implanted the distal end of the duodenum at various levels in the jejunum after the proximal end was closed. Kiriluk[112], Woodward and his associates[164] tested the sensitivity of tissue to ulceration at various levels of gastrointestinal tract, with a stream of pepsin solution. They concluded that the esophagus is the least resistant, the antrum and fundus are the most resistant parts of the gastrointestinal tract. Duodenum, jejunum and ileum are intermediate, and the colon is the most susceptible because the muscularis mucosa is most readily penetrated. They also noticed that there is a progressive decrease in pH and buffering capacity from the pylorus. The incidence of ulceration in different parts of the gastrointestinal tract was reported by McMaster[136]. He obtained 45% ulceration in the jejunum, 80% in the ileum and 100% ulceration, mostly haemorrhagic, in the colon.

Mann[146] in his experiment used loops of duodenum, jejunum and ileum and transplanted them to the point of emergence of gastric contents in Mann-Williamson dogs. The duodenal mucosa was found to be most resistant to the formation of ulcer and mucosa of ileum least resistant. McCann[130] and Fauley[53] concluded that this protection might be due to the mucoid

FIGURE 4f



Procedures to study the role of mucosal susceptibility and mechanical factors.

secretion of Brunner's glands. They modified the Mann-Williamson procedure so that the first part of the duodenum was anastomosed to the jejunum and the rest of the duodenum was drained into the ileum. Ulcers occurred only in the jejunum and not in the duodenum.

Morton[131] in 1927 demonstrated jejunal susceptibility by producing ulcers at the lesser curvature using the Mann-Williamson procedure. This ulcer healed if gastroenterostomy was done, but a new ulcer formed in the jejunum or at the stroma.

Wangensteen and associates with three-quarters gastric resection produced no ulcers, even after giving histamine in beeswax. They concluded that increased susceptibility of the intestinal mucosa increases as the distance from the pylorus increases. In considering the etiological factors for ulceration in these types of preparation, the following four factors should be considered: -

1) Secretin concentration is lower in the lower part of the bowel.

2) Spatial relation of acid and alkali in digestive juice.

3) Mucosal sensitivity.

4) Nutritional factors.

Wu and Mann[102] produced ulceration in the ileum after implanting a portion of the stomach in two or three stages to the ileum. Similar results were obtained by Wu and Thompson[225] in producing ulcers in the ileum. They modified the previous preparations by draining the stomach portion separately with a segment of bowel into the ileum.

Interposition of a bowel segment between the stomach and the duodenum for experimental production of ulcer was first performed by Schoemaker[75] in 1911. Fiori[193] in 1913 after gastric resection used jejunal or colonic transplants and described the procedure as "a plumber inserting

a short section of pipe between two others." Fiori did not produce any ulcers. He concluded that some extra factor entered in when the juice leaves the stomach to run into a loop of bowel. It is reported that Kuprijanow in 1924 produced ulcers with the same technic. Harrison and his associates[192] in 1958 inserted an ileal implant between the first and second portions of the duodenum. After a 24 week period of observation 7 out of 9 dogs were found to have chronic ulcers in the ileal insert.

E) Mechanical factors in the production of peptic ulcer (Fig. 4f)

Mann and Flood[57] considered propulsive action of the stomach as an important factor in the production of ulcer. In his experiment he reduced the incidence of ulceration by constructing an hourglass stomach. Other experimentors attached significance to the size of the anastomotic opening[201], gastric motility[16] and the type of bend at the anastomosis. It is reported that Deloyer stressed the mechanical factor as of less importance because in his experiment he placed a patch of jejunum in the stomach of the Mann-Williamson dog. Ulcer occurred only opposite the gastrojejunostomy opening and not in the patch, although conditions were identical for both. Operative trauma with the application of clamps produces acute ulcers, but the lesions occasionally go on to chronicity[69, 72]. The use of sutures, especially silk, was considered by some as an etiological factor in ulcer production, but in experiments of Scott[184] with the use of silk sutures this was found not to be a significant factor. Jejunal spasm was considered by Stenberg and Starr[185] as a factor for ulcer production. In their experiment they stripped the jejunal musculature for a distance of 10 cm. distal to the anastomosis. No ulcer occurred at the stripped area, but proximal to it. However, other experimentors developed ulcer in the stripped area in a similar preparation[53].

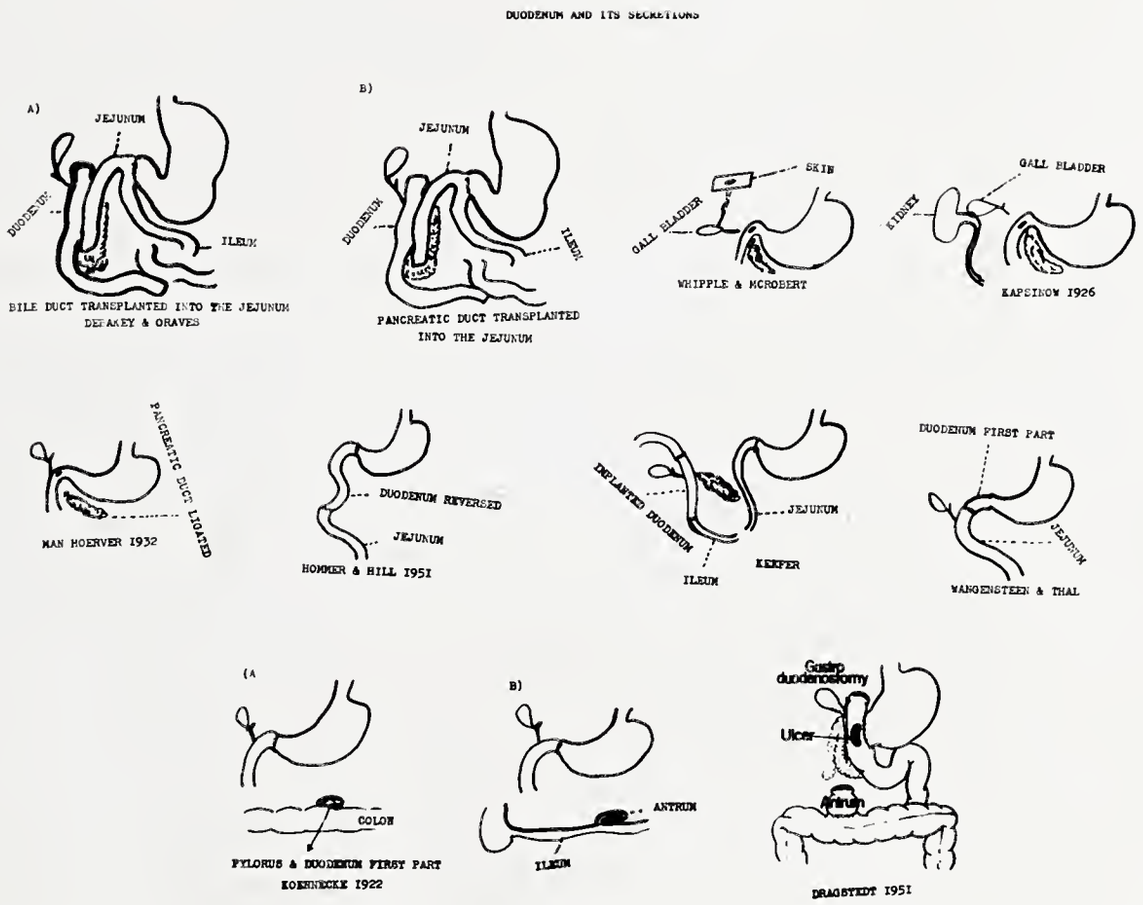
F) The role of duodenal secretions and the antrum in the etiology of peptic ulceration (Fig. 4g)

Secretion of Brunner's glands, bile and pancreatic juice all have a protective action in the development of peptic ulcer. It was stated that ulcer will form whenever the gastric juice strikes the intestinal mucosa, when the bile and pancreatic juice had not previously arrived at the same site. Debakey[36], Graves[71] and other experimentors[17, 7], in order to determine the individual role of bile, pancreatic juice and duodenum performed various experiments. In one group of dogs the bile duct was transplanted to the jejunum at the site of gastrojejunostomy after the duodenum was drained to the ileum. In other groups the pancreatic duct was transplanted instead of the bile duct. All dogs developed ulcer. Other experimentors implanted duodenal segments containing bile and pancreatic duct into ascending or transverse colon. This resulted in ulceration at the proximal duodenal suture line.

It is reported that Whipple and McRobert[4] developed occasional ulcer after draining the gall bladder outside the body by a fistula. Kopsinow[4] in 1926 got a similar result by draining the gall bladder into the pelvis of the right kidney.

Mann and Hoerver[4] in 1932 developed occasional ulcer by ligating the pancreatic duct. Hammer and Hill[86] in 1951 modified the Mann-Williamson procedure by reversing the duodenum, acute ulcers developed in 2 to 6 weeks. Dogs with duodenectomy lived for 1½ to 2 years in good condition. Two out of 10 dogs developed ulcer[133]. These experimentors concluded that bile is the most important, pancreatic secretion intermediate and succus entericus or duodenal secretion least important in the production of peptic ulcer.

FIGURE 4g



Procedures to study the role of duodenum and antrum.

Experiments of Keefer and his associates[117] stressed the importance of duodenal juice, or Brunner's gland secretion, or a hormone which had protective action. They anastomosed an isolated segment of duodenum and anastomosed it end to end isoperistaltically to the distal ileum, retaining the physiological functions of the duodenum. No ulcer developed. In addition to duodenal hormone they also believed in selective absorption of the intestinal tract to prevent ulcer.

Experiments of Thal and Wangensteen[18, 19] show that resection of the duodenum with anastomoses of pancreatic and bile duct to proximal 20 cm. jejunum results in a marked increase in the Heidenhain pouch hydrochloric acid secretion. They concluded that this might be due to loss of an inhibitory control on gastric secretion. The nature of this control mechanism is not yet clear at the present time.

The effect of total pancreatectomy and external pancreatic fistula on gastric secretion and ulcer production was studied by Dragstedt and his associates[37] and Poth[165, 166]. The alkaline pancreatic secretion was deviated from duodenum by external pancreatic fistula, ligation of pancreatic duct or by implantation of pancreatic duct into lower reaches of gut, without removal of the pancreas. Total pancreatectomy produced ulcers, but less frequently than did drainage of the pancreas by external fistula. Total pancreatectomy produced a significant increase in gastric secretion from Heidenhain pouch. It was suggested by Poth that this difference might be due to the fact that the hyperglycemia after pancreatectomy suppresses gastric secretion sufficiently to protect the gastroduodenal mucosa from ulceration. Dragstedt concluded that insulin or some other hypoglycemic factor in the pancreas may play a very important role in ulcer production.

Slight regurgitation of duodenal secretion into the stomach and proper functioning of the sphincter of Oddi were considered by some as an essential factor in the production of ulcer. Section of the sphincter of Oddi lowers the incidence of histamine induced ulceration in cats[176]. The role of sphincter of Oddi in the etiology of peptic ulceration in dogs is not known at the present time.

It is reported that Koennecke[4] in 1922 tried to produce ulcer by implanting the first part of the duodenum and pylorus on the colon. He later did splanchnicotomy to prevent ulcer formation. All his animals died. He was successful in producing gastrojejunal ulcer after implanting antrum to terminal ileum. In 1951 Dragstedt and his associates[39, 186] demonstrated that transplantation of the antrum into the colon resulted in a profound increase in gastric secretion. Eighty percent gastric ulcer developed when intestinal continuity was made by gastrojejunostomy. Only 20% gastric ulcer occurred with gastroduodenostomy. The presence of food or fecal material in the antrum was believed to be a stimulus for gastric hypersecretion and ulcer production[88]. It is now a well established fact that when the antrum is left to bathe in alkaline secretion it increases gastric secretion with the release of gastrin[38]. The procedures of antral exclusion like those of Eislsburg and Devine produce ulcers consistantly in dogs.

CHAPTER IV

EXPERIMENTAL PRODUCTION OF PEPTIC ULCER BY USE OF ILEAL IMPLANT

A. INTRODUCTION

Since 1890 the effect of operative procedures on the incidence of experimental ulcer has been studied in the hope that it would clarify its etiology, and assess the effectiveness of surgical treatment. Boronofsky[10] investigated the percentage of gastric resection required to protect animals from histamine induced ulcer. Thal[211] investigated the effect of operative procedures on pouch secretion. Other experimentors attempted to study the effect of various operative procedures on the incidence of experimental peptic ulceration[183]. Thal's experiments are a measurement of blood borne gastric stimulants, and so does not explain the exact factors for the production of ulcer. Histamine acts by stimulating the parietal cells directly and may not have any bearing on clinical peptic ulcer[50]. Because histamine probably stimulates the parietal cells directly, its use in procedures which remove the parietal cell mass will show a low incidence of ulcer[105]. The Mann-Williamson procedure produces chronic ulcer, but interferes seriously with nutrition of the animal. Nutritional factors themselves favor ulcer production and may increase parietal cell secretion.

An ideal ulcerogenic preparation should satisfy the following criteria: -

1. Produce chronic ulcer consistently.
2. The animal's nutrition should not be seriously disturbed.
3. Exogenous drugs such as histamine should not be required.
4. Anatomy of the gastrointestinal tract should be minimally disturbed.
5. Pylorus should be retained.

We believe our experimental method satisfies these

requirements and that it is a useful tool for studying the ulcer protecting properties of the presently employed procedures for duodenal ulcer. Specifically it has enabled us to assess the protection offered against recurrence by vagotomy, and also made it possible to study the role of the antrum in the production of ulcer.

B. METHOD

All male dogs were used, weighing from 12 - 20 kilograms. Preoperative preparation consisted of deworming the intestinal tract with Virmiform tablets, (one tablet per pound of body weight). Nothing was given by mouth for one day prior to the operation. Postoperative care consisted of: -

1st day	No food given by mouth
	250 to 300 cc. electrolyte solution or 10% glucose in water intravenously
	Crystalline penicillin 600,000 units with 0.5 grams
	Streptomycin intramuscularly
2nd day	Small quantity of water 2 to 3 times daily (total 50 - 75 cc.) by mouth
	250 cc. electrolyte solution or 250 cc. 5% glucose in saline solution
3rd & 4th day	Milk and water at 6 hour intervals
	1.5 cc. dicrystecin - crystalline penicillin, 600,000 units with 0.5 grams streptomycin instramuscularly
5th & 6th day	Small quantity of meat, milk and water
7th day	One-half can of regular dog meat, milk and a small quantity of regular food
8th day onward	Regular diet (Miracle precooked dog food*, meat and water).

* The Ogilvie Flour Mills Co. Ltd.

C. OPERATION AND PROCEDURE

At operation 250 cc. of glucose and water were administered by the intravenous route during the procedure. The animal was anaesthetized with sodium phenobarbital, 35 milligrams per kilogram of body weight. With all aseptic precautions the abdomen was entered with a midline incision. The first part of the duodenum was mobilized and brought into the wound. It was transsected distal to the pylorus, taking care not to disturb the biliary or pancreatic ducts. A 15 - 20 cm. length of terminal ileum was isolated and continuity of the terminal ileum was re-established by end to end anastomosis. The ileal mesentery was closed. The segment of ileum was interposed with end to end anastomosis isoperistaltically between the divided segments of the first portion of the duodenum (Fig. 5). All anastomoses were made in two layers using No. 3 and No. 2 chromic catgut. The abdominal wound was closed in layers using No. 3 catgut for the peritoneum, interrupted cotton sutures for the fascia and No. 2 catgut for the subcuticular skin closure.

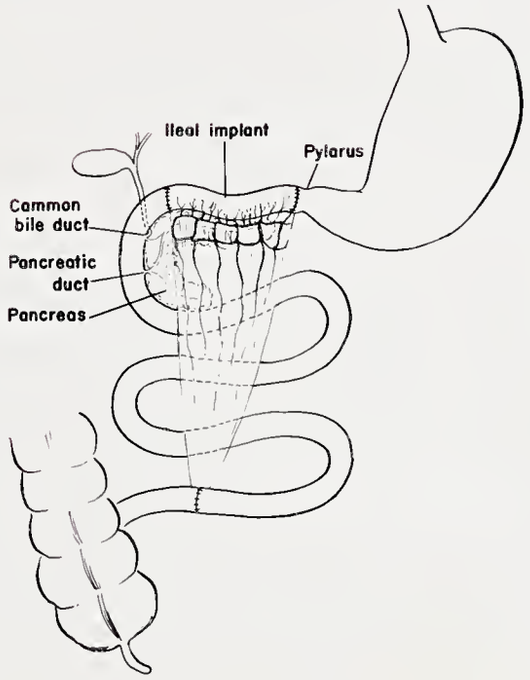
Stools were tested for occult blood once weekly using hematest tablets*. If the animal did not die of haemorrhage or perforation it was sacrificed if the stools consistently showed occult blood. In our series the interval between the operation and the postmortem varied from five to twenty-four weeks.

D. RESULTS (Table I)

Seven dogs out of nine developed large chronic ulcers. They were located on the anterolateral aspect of the implant close to the proximal suture line. One of the animals died of perforation. The gross and the microscopic sections of the ileal ulcers are shown in Figures 6 and 7.

* Ames Company Incorporated

FIGURE 5



Operative Method of Ileal Insert

TABLE I

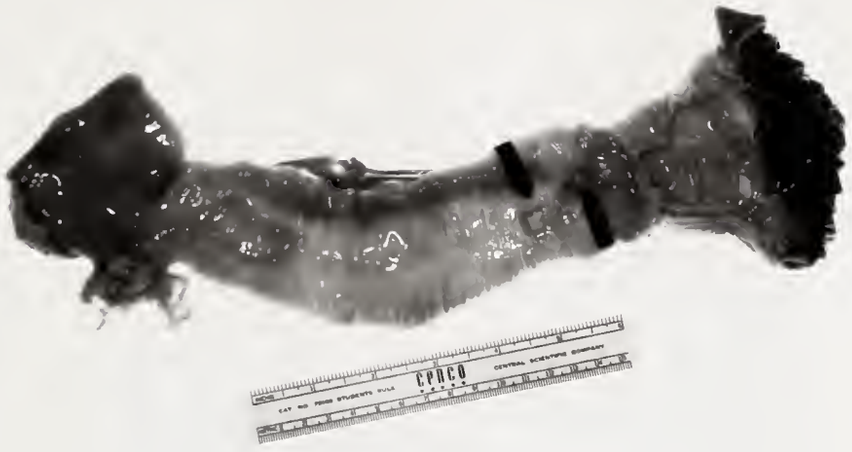
Table I

Dog No.	Length of implant.	Post-op. survival period. (Sacrifice or death)	Gross ulcers.	Period of occult blood in stools, prior to sacrifice or death.
9	15 cm.	90 days	+	16 days
12	18 cm.	92 days	+	28 days
65	24 cm.	46 days	*+	14 days
66	40 cm.	67 days	+	20 days
1	42 cm.	98 days	-	14 days
72	42 cm.	132 days	+	90 days
3	43 cm.	166 days	+	48 days
68	45 cm.	37 days	+	9 days
71	50 cm.	48 days	-+	14 days

* perforated ulcer.

Results of ileal insert procedure

FIGURE 6



Gross examination of ileal implant
with chronic ulcers

FIGURE 7

Microscopic section of ileal implant ulcer

To study the possible effect of the ileal insert procedure on the gastric secretion, Heidenhain pouches were constructed in four animals. Four to six weeks following creation of the pouch, 24 hour pouch secretions were collected for two weeks and hydrochloride and total chloride output was determined. The ileal insert procedure was then done, and after four weeks the pouch secretion was again determined for a two week period. The results were equivocal; two animals showed an increase and two animals showed a decrease in Heidenhain pouch secretion of free acid and of chloride (Table II).

TABLE II

Dog No.	Heidenhain Pouch Secretions (24 hrs.) of Free Acid (mEq/Vol)		Postop (Ileal Transplant) Heidenhain Pouch Secretion as Percentage of Preop Heidenhain Pouch Secretion
	Before "Ileal Transplant"	After "Ileal Transplant"	
47	32.3	69.2	214%
55	17.8	9.4	52%
65	3.3	2.2	67%
67	13.5	31.4	232%

Effect of Ileal Insert on

Gastric Secretion

CHAPTER V

A CRITICAL APPRAISAL OF PRESENTLY EMPLOYED PROCEDURES FOR DUODENAL ULCER AND AN ATTEMPT TO ASCERTAIN THE COMPARATIVE VALUE OF THESE EXPERIMENTALLY

A. INTRODUCTION

The surgical management of duodenal ulcer and its complication is controversial and has been the subject of vigorous debate for many years. Not only are the indications for surgical intervention challenged, but also the choice of operative procedure.

All the presently employed procedures lack uniform success. Also the operative mortality, immediate morbidity and the frequency of recurrent ulceration must be considered. As Ian Aird[2] said "Every operation the surgeon performs for ulcer is an experiment, even though it is a logically necessary and probably desirable experiment, and to examine his results profitably for his patient, and for his art he must have a background of theoretical knowledge against which to view the effects of his work."

B. HISTORY OF DEVELOPMENT OF PROCEDURES

New surgical procedures for duodenal ulcer have been advanced frequently since 1880 when gastric surgery began, but most of them have proved unacceptable. Billroth in 1881 performed the first successful gastrectomy which had been unsuccessfully attempted by Pean in 1879. Gastric resections were originally developed primarily for cancer and later carried over to the treatment for duodenal ulcer.

Gastroenterostomy alone was used extensively during the fifty year period 1885 - 1935, but abandoned due to the high ulcer recurrence rate (30 - 40%)[154]. During the first two decades of this

century few surgeons cared to dispute the statement made by Moynihan[2] in 1908 that "No operation has been more completely satisfactory than gastrojejunostomy". As late as 1925 Sherren[187] said that "It has done more than any other operation for the good of the human race." Gastroenterostomy alone is frequently followed by duodenal ulcer in the dog, an animal which does not develop a chronic duodenal ulcer under normal conditions[89].

In 1915 Von Haberer first introduced partial or subtotal gastrectomy for the treatment of duodenal ulcer, and since the 1930's subtotal or partial gastrectomy has become the procedure of choice in the hands of most surgeons. The problem of ulcer recurrence was successfully solved by a 75% gastric resection. The excellent result of partial gastrectomy for stomal ulcer by Wells[230] converted British surgeons to this operation as a primary treatment of duodenal ulcer. With the advent of gastric resection one famous surgeon[2] in the 1930's remarked "If any surgeons wanted to remove four-fifths of my normal stomach to cure a small ulcer of my duodenum, I would run faster than he." Although gastric resection has reduced the ulcer recurrence problem to a minimum, to remove a healthy part of the stomach is not a real solution to the problem. Probably in the future this era will be looked back on as the dark age of gastric surgery.

As more and more stomach was removed to reduce the incidence of stomal ulcer, the incidence of postoperative sequelae rose and it was later realized that ulcer recurrence could not be kept below 5% without getting some postoperative sequelae. Seventy-five percent resection with gastrojejunostomy is associated with the lowest incidence of ulcer recurrence[177]. The advancement in surgical technics, as well as better post-

operative care have made gastric resection a less dangerous procedure than before. Up to 90% obtained excellent results[90].

The procedures of antral exclusion which were developed by Eiselsberg in 1895, Finsterer in 1918 and Devine in 1928 were advocated to avoid closure of the technically difficult duodenum. In these the antrum is left in contact with alkaline secretion which markedly stimulates acid production, leading to a very high incidence of ulcer recurrence.

Vagotomy was introduced by Dragstedt and Owens in 1943 for use in duodenal ulcer[5]. Its combination with[a] drainage procedure (gastrojejunostomy)was used by Dragstedt in 1945 and with Heinecke - Mikulicz pyloroplasty by Weinberg in 1953[2]. Vagotomy with hemigastrectomy (45% resection) with Billroth I or Billroth II anastomosis was advocated by Smithwick, Harkins[85], Zollinger and Stock[188] in the 1950's. It was hoped that the addition of vagotomy would give better protection with less radical gastric resection, but it is not yet clear how much protection it adds to procedures which by themselves are followed by a high recurrent ulcer rate. It is claimed that vagotomy with drainage procedure gives a high incidence of satisfactory results with the lower surgical mortality and morbidity in patients with chronic duodenal ulceration.

Recent work on the gastric antrum added a further acceptable operative procedure for duodenal ulcer. Segmental resection, a modification of earlier sleeve resection in which 50% parietal cell mass is removed, was advocated by Wangensteen[228] in 1949. Tubular resection was also introduced by Wangensteen in 1940. Tubular resection or pie resection is a modification of Connell's[26] operation in 1929 termed "fundusectomy" in which only 40% of the parietal cell mass was excised, and antral innervation preserved.

Recently in order to overcome the problem of dumping and to increase gastric capacity after radical gastric resection for duodenal ulcer, an intestinal interposition operation was popularized. It is claimed that this operation of interposition was first performed by Schoemaker in 1911. Experimental work done by Kuprijanow in 1924 led to its clinical use by Sacharow[193] from 1938 - 1948 and Henley[75] in 1952. A limited number of patients with a short term follow-up of two years were treated in the Crimea, Russia[193].

C. OPERATIONS FOR DUODENAL ULCER CAN BE CLASSIFIED INTO THE FOLLOWING GROUPS:-

1. Drainage operations:
   a) Gastroenterostomy and vagotomy.
   b) Pyloroplasty and vagotomy.
2. Resection of fundus:
   a) Segmental resection (Wangensteen I).
   b) Segmental resection and vagotomy.
   c) Segmental resection with preservation of the vagus at lesser curvature (Ferguson).
   d) Tubular resection (Wangensteen II).
3. Mucosal resection (Williams[218])
4. Resection of antrum and varying percentage of fundus:
   a) Antrectomy
   b) Antrectomy and vagotomy
   c) Hemigastrectomy
   d) Hemigastrectomy and vagotomy
   e) Billroth I
   f) Billroth I and vagotomy
   g) Polya
   h) Polya and vagotomy

D. APPRAISAL OF OPERATIVE PROCEDURES, POSTOPERATIVE PROBLEMS AND MORTALITY

The currently employed operative procedures for duodenal ulcer can be classified as having either one or two of the following as their primary aim.

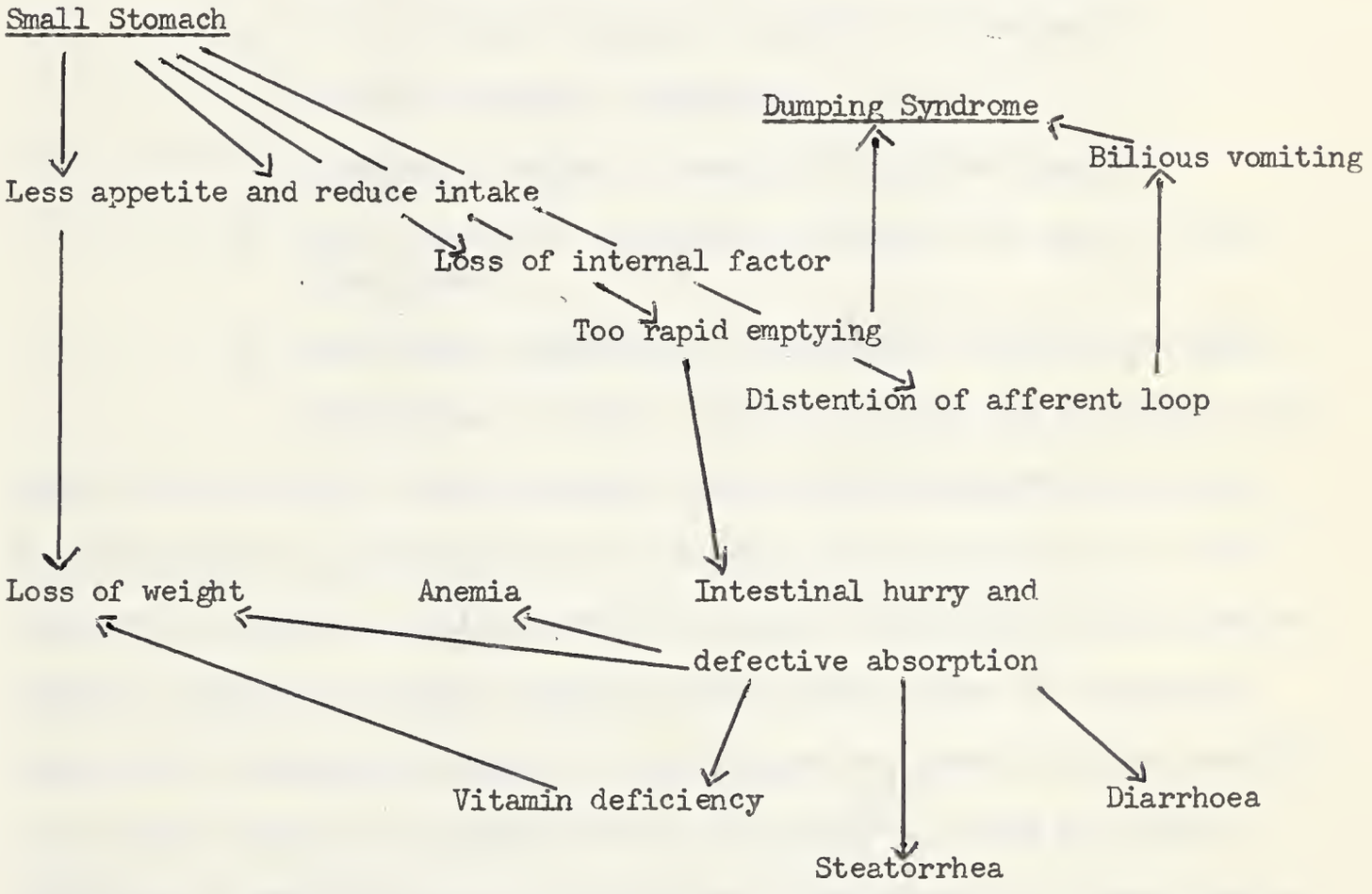
1. Vagotomy
2. Preservation of the vagus
3. Antrectomy
4. Antral preservation
5. Excision of the acid secreting parietal mucosa
6. Maintaining the storage capacity of the stomach

In these operations the antrum is preserved in group 1, 2, 3. The vagal innervation of the acid secreting portion of the stomach is divided in group 1, group 2 (a, b), group 4 (b, d, f, h), and vagal supply preserved in group 2 (c, d), group 3, group 4 (a, c, e, g). The procedures in group 2 (c, d) are designed specifically to preserve the vagal supply to the gastrointestinal tract. Group 3, 4 (c, g), 2 (a) have as their primary aim the excision of acid secreting parietal mucosa. Group 3 is primarily for excision of acid secreting parietal mucosa and also to increase storage capacity of the stomach.

It is very difficult at this time to obtain from surgical literature an acceptable appraisal of currently employed procedures because each group differ on basic principles. For example, Wangensteen's group believe in producing achlorhydria as the best method of protection from ulcer recurrence, whereas Dragstedt's group believe in correcting only the secretory abnormality by reducing acid and volume of the gastric content during the interdigestive phase within normal limits. The third group lay stress on the relation between pH and peptic activity; if the pH of gastric

content is 4.5, 5 or over the likelihood of peptic ulceration would be negligible[62]. None of the procedures mentioned are free from postoperative sequelae. The more radical the procedure is, the more the incidence and severity of postoperative sequelae. In planning duodenal ulcer operation the surgeon has to decide for the patient between a small stomach with less risk of stomal ulcer and dumping syndrome, and a large stomach with more risk of stomal ulcer. The following diagram illustrates the cycle of changes that could take place in the body with a small stomach and dumping syndrome[59].

FIGURE 8



The data of postoperative sequelae is available for the old procedures, but not for those developed during the past decade. The available surgical literature does not clearly mention either the post-operative sequelae or the ulcer recurrence rate for each of the operations for duodenal ulcer. The essential data required to evaluate each operative procedure is as follows: -

1) Weight - optimum, maximum, pre and postoperative
2) Appetite - pre and postoperative
3) Fatigue - ability to resume their previous occupation
4) Early post-cibal dumping - severity and frequency
5) Late post-cibal dumping - severity and frequency
6) Bilious vomiting - frequency
7) Diarrhoea - number of stools in a 24 hour period
8) Food - degree of restriction necessary for each of these procedures.
9) Nutritional deficiencies - peripheral neuritis and edema.

Considering the above factors, at least 75% of patients will admit to one or more of these symptoms early in the postoperative period. The frequency and severity diminish with time and at the end of two years only 40% will admit to less than perfect results. Radiological and electrographical studies of gastric resections with various types of anastomosis suggest that gravity and change of pressure upon the stomach during breathing are the main factors for postgastrectomy emptying[100]. There was little difference in emptying among the main types of anastomosis. Fisher, Taylor and Cannon[64] in 1955 devised a test for studying the dumping syndrome and found that after either vagotomy and pyloroplasty or Billroth I resection the incidence of dumping was 29%, and after Billroth II it was 48%. The

postoperative symptoms were more frequent with Billroth II or with the Polya type of anastomosis, because the physiology and anatomy of the gastroduodenal area were seriously disturbed.

Regarding ulcer recurrence, a long follow-up of at least 10 years is necessary. Again only the older procedures can be evaluated correctly at this time. Melena, ulcer pain and other ulcer symptoms usually require a long follow-up before it becomes a proven recurrence. The history of gastroenterostomy itself demonstrates the need of a long follow-up. Walters[240] has shown that 34% of patients develop stomal ulcer following gastroenterostomy after a 5 year follow-up visit. This shows that probably a compensatory acid stimulating mechanism develops in parietal cells, as shown by fractional gastric analysis[123]. It is also demonstrated that hypertrophy in the gastric remnant occurs after 66% gastric resection[73].

The high incidence of recurrent duodenal ulceration in some series of the Billroth I operation might be due to inadequate gastric resection. Ulceration on the stomach side was much more common after Billroth I than with Billroth II gastric resection[155]. Another disadvantage with Billroth II anastomosis is that the proximal jejunum used for anastomosis is less resistant to acid peptic digestion in comparison to the duodenum which is used for Billroth I [142].

Figures from the Cleveland Clinic show a 7% incidence of stomal ulcer following vagotomy and gastroenterostomy at 2 years, 12% incidence at 3 years and a 17% incidence at 8 years[101]. Fallis[96] reports a 2½% incidence on a 5 year follow-up with hemigastrectomy and vagotomy. Harvey et al[100] from the Presbyterian hospital, New York, reports a 1 to 7% recurrence of ulcer. The length of the follow-up period is not mentioned.

It is reported that Scott and Harkin[96] have an insignificant incidence of recurrence following vagotomy and hemigastrectomy. Burdette[23] from Utah and Stock[188] from Hong Kong reported an insignificant incidence of recurrent ulceration during a short follow-up with vagotomy and antrectomy, vagotomy and pylorectomy (one-third gastrectomy) respectively. Wangensteen[214] with tubular resection had an incidence of stomal ulcer of only 3% with 3 to 6 years follow-up, and with segmental resection had only three stomal ulcers in 500 cases. The follow-up period was not mentioned.

Experimental results show that marginal ulceration occurs earlier and oftener after gastrojejunostomy than after gastroduodenostomy. It is interesting to know that stomal ulcer takes longer to show after gastrojejunostomy than after gastric resection[216]. Walters[215] in his study of 301 cases analyzed gastrojejunal ulcer and found 96.3% developed after duodenal ulcer operation, 2% from gastric ulcer operation and 1.7% from both.

Wangensteen and his associates[241] attempted to evaluate the individual operative procedure clinically on the basis of effective reduction in gastric acidity, and also in preventing recurrent ulceration. They found that achlorhydria with triple stimulation with histamine was not achieved after any type of operation.

Among all the various surgical procedures used the best results with regard to recurrent ulceration and dumping were obtained with gastric resection and vagotomy. At the Mayo Clinic subtotal gastrectomy is among the present methods most widely used in the surgical management of complicated or intractable duodenal ulcer[217]. In about 11% of patients

other less radical procedures such as pyloroplasty, both with and without vagotomy have been used. The reasons for adding vagotomy to partial gastric resection at the Mayo Clinic are: -

1) Patient considered good candidate for jejunal ulceration.

2) Technical difficulties or poor risk patient which indicates less radical resection.

Mortality from these various procedures varies with the magnitude of the operative procedure and with the age of the patient ranging from $\frac{1}{2}$ to 3% in experienced hands[96]. It is reported that Tanner had 0.6%, Vesick 3.7%, Lake 5.7% and Wells 2% mortality after gastric resection for duodenal ulcer[96]. Hener[97] had a 7% mortality in his whole series of 142 gastric resections. Stock[188] from Hong Kong had 2.1% mortality with vagotomy and pylorectomy (three-quarters gastrectomy).

C. THE EFFECT OF STANDARD SURGICAL PROCEDURE ON ACID PRODUCTION

1) Gastroenterostomy

The incidence of stomal ulceration in the human following gastroenterostomy is 35%. The high incidence of ulceration probably is due to alkalinization of antral mucosa with duodenal contents with a resultant increase in acid production.

Experiments of Dragstedt and his associates[158] prove that high gastroenterostomy stimulates gastric secretion by alkalinization of stomach content, but does not effect when the stoma is located at the antrum. The increase in acid production does not occur if drainage is accompanied by pyloroplasty. Day and Webster[35] have demonstrated that the presence of acid chyme in the duodenum is an important factor in the autoregulation of gastric secretion, the inhibitory effect thus found normally may well be lost when acid chyme is diverted away from the duodenum by means of gastro-

jejunostomy. It is important for surgeons to realize that drainage procedures in themselves have an effect on acid secretion, and are likely to increase the incidence of stomal ulcer[96].

2) Vagotomy

Complete vagotomy eliminates the cephalic phase, but prolongs the humoral phase by stasis. This paradoxical effect of vagotomy can be controlled by low gastroenterostomy. A high gastroenterostomy with vagotomy will increase pouch secretion and hence increase the likelihood of stomal ulcer[96]. Vagotomy by decreasing the tonicity and motility of the stomach gives striking and persistent relief of ulcer distress[46]. Vagotomy appears to reduce duodenal inhibition of acid secretion[208]. The effect of vagotomy is complete if all of its fibres are divided. The possibility of regeneration between one to three years after surgery[62]. Experimental studies show that vagotomy or vagotomy and gastrojejunostomy do not protect against duodenal ulcer or erosion produced by chronic histamine stimulation[22]. It was suggested that this may be due to trophic disturbances of the gastric and duodenal wall by vagotomy. Dragstedt and his associates[232] postulated the theory that vagotomy reduces the acidity in the main stomach and thereby decreases acid inhibition of antrum function. Dragstedt[47] believed that the explanation is largely due to gastric retention and in his experiment this effect was lost with the addition of a drainage procedure. It is now believed that in duodenal ulcer patients cephalic or neurogenic phases of acid secretion are controlled through the vagus and are solely responsible for the heightened acidity. When vagotomy is performed the neurogenic phase is abolished, leaving only the humoral phase to carry on the function of acidification. This phase is relatively non-

corrosive owing to admixture with food. It is this alteration in acidity which is the basis of treatment of duodenal ulcer by vagotomy. Vagotomy alters the pyloric sphincteric action, with the result that gastric emptying is delayed. Because of gastric stasis some type of drainage procedure is essential. The drainage procedure of choice would be pyloroplasty rather than gastroenterostomy. A most interesting and as yet unanswered question is the possible direct or indirect relationship between the vagal hyperactivity and underlying emotional disorders[110].

The complications of vagotomy are as follows[2]: -

1) Vomiting (severe in 13% of cases)
2) Gastric distention (15% require subsequent drainage operation).
3) Dysphagia due to interference with esophageal musculature.
4) Paralytic ileus.
5) Diarrhoea, probably due to stasis, fermentation of food, changes in bacterial flora in the gut (severe in 16% of cases), and pancreatic secretion deficiency.
6) Recurrence of duodenal ulcer after 5 years in 28%[205].
7) Loss of weight (less than after gastric resection).
8) Gastric ulcer (vagotomy should not be done for patients who have duodenal as well as gastric ulcer, or who have gastric ulcer alone).
9) Decrease in pancreatic secretion.
10) Diaphragmatic hernia due to stretching of the hiatus.

3) <u>Antrectomy and limited fundus resection</u>

Acid secreting cells are chiefly in the body and fundus of the stomach, distributed to the entire stomach except the antrum. The antrum normally secretes mucus[20]. Wangensteen once remarked that if the antrum was situated normally at the proximal end of the stomach, its removal would not have been so universal. Several combinations of operative procedures with

antrectomy, vagotomy and partial resection of the fundus have been tried in order to prevent recurrent ulcer rate and also to avoid postoperative effects from radical gastric resection. To retain the reservoir function of the stomach especially with people eating bulky rice diet in Hong Kong, the procedure of vagotomy and pyloroplasty (one-third gastrectomy) was adopted as a routine procedure in Hong Kong for duodenal ulcer since 1952[188].

Due to the small series and inadequate follow-up time it is difficult to assess the procedures at the present time. Further clinical and experimental work will clarify the situation. Experimental and clinical investigations show that removal of the antrum with a small portion of secreting mucosa is an inadequate operation for duodenal ulcer[5]. The innervated antrum is more sensitive to chemical and mechanical stimuli than the denervated antrum[211]. This concept is further supported by the work of Savich[6] who demonstrated that cocainization of the antrum reduces its hormonal activity. It has not been proven that an active inhibitor is produced by the antrum, and at what pH it works. It has also not been proven whether this mechanism exists in the human and how vagal denervation affects it. One thing about the antrum which has been proven, is that the antrum if left bathed with alkaline secretions results in a very high incidence of recurrent ulceration[89]. Any operative procedure which decreases the acidity in the region of the antrum results in an increased acid production by the body of the stomach and is ulcerogenic, the reverse is also true.

4) Resection of the fundus and antrum preservation

Wangensteen advocated two procedures in which only the acid producing fundic portion of the stomach is removed and the antrum preserved. Tubular resection or pie resection has some advantage in that pyloric reflex and duodenal control of gastric secretion are preserved[214].

It is reported that tubular resection is followed by a significant percentage of ulcer. Segmental resection vagotomizes the patient; it has the advantage of eliminating the problem of the difficult duodenum[48]. Pyloroplasty added to segmental resection facilitates emptying of the gastric pouch. Heidenhain pouch secretions in animals show that the marked secretory effect which characterizes the tubular gastrectomy is uniformly absent in segmental resection. It is interesting to know that the stomach pouch in both operations is made up principally of the fundus and antrum of the stomach; however, the tubular operation differs in that the strong pepsin secreting area of the lesser curvature and vagal supply to the antrum remains intact, whereas in the other procedure the antrum is denervated. Moreover closure of the tubular resection by transverse gastroplasty creates a physiological antral exclusion operation. The 5 year follow-up study of segmental resection is satisfactory[211].

5) Gastric resection and intestinal interposition

The operation for trying to restore the capacity of the stomach by interposing a segment of bowel or colon after radical gastric resection did nothing to reduce acidity or affect neutralization[144]. Reports on patients treated and followed for two years with interposition of a segment of bowel from the hospital surgical clinic in the Crimea, Russia, show good functional results and with no ulcer recurrence[145]. This operation sounds more physiological than the Billroth II procedure and is satisfactory if there is consistent achlorhydria, but in experimental animals achlorhydria was not achieved with any operative procedure after triple stimulation with histamine[241]. Other experimentors in order to increase the capacity of the stomach and prevent kinking used a pantaloon-type anastomosis of the jejunum. The results reported are not satisfactory[206].

F. CONCLUDING REMARKS

There is no general agreement among clinicians or investigators regarding the relative merits of these many operative procedures. The surgeon knows his main objective is to prevent recurrence of ulcer. This was difficult as he did not know how the ulcer came about, what was demanded of a satisfactory operation, or how his procedures were going to affect the natural history of the disease. Baronofsky[8] showed that after histamine in beeswax 75% gastric resection was required to protect the animal from ulcer, whether the operation was carried out on the Billroth I or Billroth II plan. Thal[211] investigated the effect of operative procedures on pouch secretion. Many attempts were made to study the effect of operative procedure and the incidence of stomal ulceration[183]. The species differ and the use of an exogenous agent might not bear true relationship with conditions in clinical patients and conclusions could not be drawn from these experiments. Ninety percent or more of the presently available procedures for ulcer control are not ideal. Past and present experience shows that there is a great deal of similarity of results in the gastrointestinal field between animals and humans. It is a real encouragement for experimentors to find that the results correlate with the results in humans. The objectives of an acceptable operation for duodenal ulcer should be as follows: -

1) It relieves the patient subjectively and removes the ulcer diathesis.

2) It prevents ulcer recurrence.

3) Reduction of the storage capacity of the stomach should be minimal.

4) Anatomic nerve supply to the gastrointestinal tract should be preserved.

5) Pyloric function should be retained

6) Normal gastroduodenal relationship should be maintained.

7) Whether or not the antrum should be saved, innervated or denervated is impossible at the present time to decide.

If an experimental procedure is to be utilized, it should upset the anatomy and physiology of the gastroduodenal area to a minimal degree. The animal's nutrition must be well maintained and exogenous drugs should not be used to stimulate ulcer production. Our experimental procedure satisfies most of these requirements, and is a useful method for studying the ulcer protecting properties of the presently employed operative procedures for duodenal ulcer.

CHAPTER VI

USE OF ILEAL IMPLANT IN THE ASSESSMENT OF CURRENT OPERATIONS FOR DUODENAL ULCER

The new procedure for the experimental production of peptic ulcer has been performed in conjunction with the standard procedures for the surgical treatment of duodenal ulcer, plus other procedures designed to investigate the role of the vagus, antrum and parietal cell mass. Table 3 lists the procedures which were employed, the status of the antrum, the status of the acid secreting mucosa and the number of dogs used in each instance. These are illustrated in Figure 10.

METHOD

Ninety mongrel male and femal dogs were used weighing from 12 to 24 kilograms. Each procedure was tested in 3 to 8 dogs. Fifty-three dogs were done by myself but the rest were included for the sake of completeness of this thesis. The details of the dogs done by myself are on Table IX. Preoperative preparations were the same as described in Chapter IV. The details regarding the individual operative procedures are as follows: -

1) Vagotomy - A standard complete vagotomy was done. Both anterior and posterior nerves were divided at the cardio-esophageal junction through the abdominal route. In some instances vagotomy was facilitated by inflating a balloon in the stomach and lower esophagus prior to isolation of the vagi.
2) Pylorectomy - The pylorus was excised with a narrow strip of distal antrum and proximal duodenum. Gastroduodenal continuity was re-established by interposing ileal segment.
3) Pyloroplasty - A Heinecke - Mikulicz type of pyloroplasty was used.

TABLE III

Proc. No.	PROCEDURE	ANTRUM	P.C.M. (Parietal Cell Mass)	No. of Dogs	No. of Ulcers
1	Pylorectomy	Preserved - Vagally Inn.	Intact - Vagally Inn.	5	5
2	Pylorectomy and Vagotomy	Preserved - Vagally Den.	Intact - Vagally Den.	5	4
3	Vagal Denervation of Antrum and Pylor.	Preserved - Vagally Den.	Intact - Vagally Inn.	4	3
4	Antrectomy	Resected	Intact - Vagally Inn.	5	2
5	Antrectomy and Vagotomy	Resected	Intact - Vagally Den.	5	2
6	Hemigastrectomy	Resected	25% Resected-Remainder Vagally Inn.	5	2
7	Hemigastrectomy and Vagotomy	Resected	25% Resected-Remainder Vagally Den.	5	1
8	Billroth I	Resected	50% Resected-Remainder Vagally Inn.	5	3
9	Billroth I and Vagotomy	Resected	50% Resected-Remainder Vagally Den.	5	1
10	Segmental	Preserved - Vagally Den.	50% Resected-Remainder Vagally Inn.	5	1
11	Segmental and Vagotomy	Preserved - Vagally Den.	50% Resected-Remainder Vagally Den.	5	2
12	Tubular	Preserved - Vagally Inn.	50% Resected-Remainder Vagally Inn.	5	5
13	Tubular and V. - same series as #11	Preserved - Vagally Den.	50% Resected-Remainder Vagally Den.	5	2
14	Radical Billroth I	Resected	75% Resected-Remainder Vagally Inn.	6	1
15	Radical Billroth I and Vagotomy	Resected	75% Resected-Remainder Vagally Den.	8	1
16	Radical Segmental	Preserved - Vagally Den.	75% Resected-Remainder Vagally Inn.	7	4
17	Radical Segmental and Vagotomy	Preserved - Vagally Den.	75% Resected-Remainder Vagally Den.	7	1
18	Radical Tubular	Preserved - Vagally Inn.	75% Resected-Remainder Vagally Inn.	3	2
19	Radical Tubular and V.-same series as #17	Preserved - Vagally Den.	75% Resected-Remainder Vagally Den.	7	1

4) Billroth I - 50% of the parietal cell mass was excised as well as the antrum. Partial closure of the gastric stroma was performed at the lesser curvature. Gastrointestinal continuity was established by interposing ileal segment. The lumen of the ileum anastomosed to the stomach was enlarged by excising the antimesenteric wall of the ileum obliquely.

5) Segmental resection - 50% of the parietal cell mass was excised, preserving the antrum, and an anastomosis performed between the intact antrum and the fundus. The segment of ileum was interposed after doing a pylorectomy between the pyloric end of the antrum and the duodenum.

6) Tubular resection - this procedure consisted of a 50% excision of the acid secreting parietal cell mass, the excision being pie shaped and extending from the level of the antrum to the fundus. The stomach was then reconstructed by a transverse closure. The nerve supply to the antrum and pylorus remains intact through the lesser curvature.

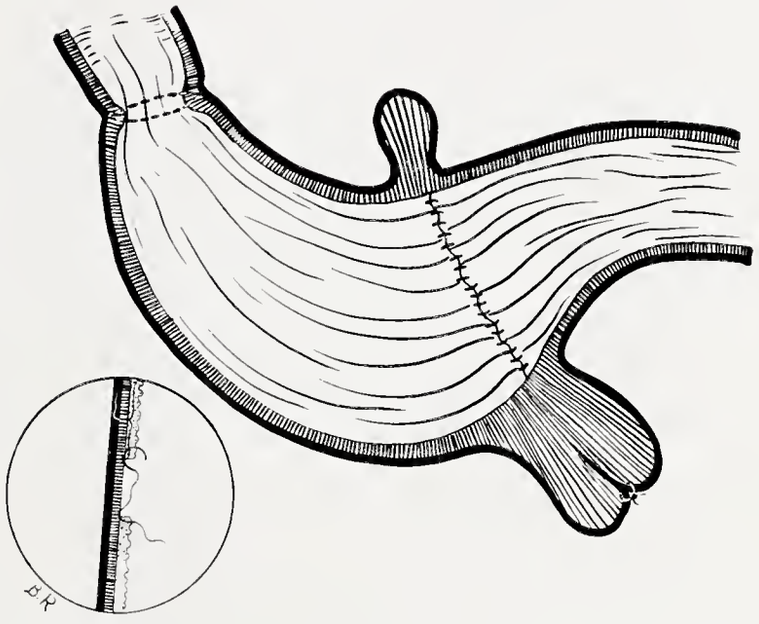
7) Tubular and vagotomy - results in the same preparation as segmental and vagotomy, so the one series of dogs was used to assess both procedures.

8) Gastric mucosal resection (Williams' procedure[218]) (Fig. 9) - This operation consisted of total excision of fundic mucosa. The antrum and pylorus were preserved with their nerve supply intact. The segment of ileum was interposed just distal to the pylorus.

9) Vagal denervation of the intact antrum was done by dividing and re-suturing the antral - body junction, plus clearing vagal fibres at the lesser curvature of the stomach.

10) Radical segmental and radical Billroth with or without vagotomy - These procedures were identical to those previously described except that 75% of the acid secreting parietal cell mass was excised.

FIGURE 9



Mucosal resection.

Due to the high mortality in radical segmental resection these procedures were done in two stages. In the first stage radical segmental resection with or without vagotomy and pyloroplasty were carried out. Two weeks later in the second stage the segment of ileum was interposed.

All anastomoses were made with 3-0 chromic catgut. The abdominal wound was closed with 2-0 chromic catgut and interrupted silk, 250 - 300 ccm. blood and 5% glucose and water, Dicrystesin 1 cc. was given intramuscularly during the operation. The routine postoperative care in these procedures consisted of the following: -

a) Crystalline penicillin 600,000 units with 0.5 grams streptomycin intramuscularly daily for 3 days.

b) Electrolyte solution No. 1 or 10% glucose and water, 250 - 300 cc. blood the second and third postoperative days.

c) Water and milk the fourth and fifth day.

d) Meat the sixth day.

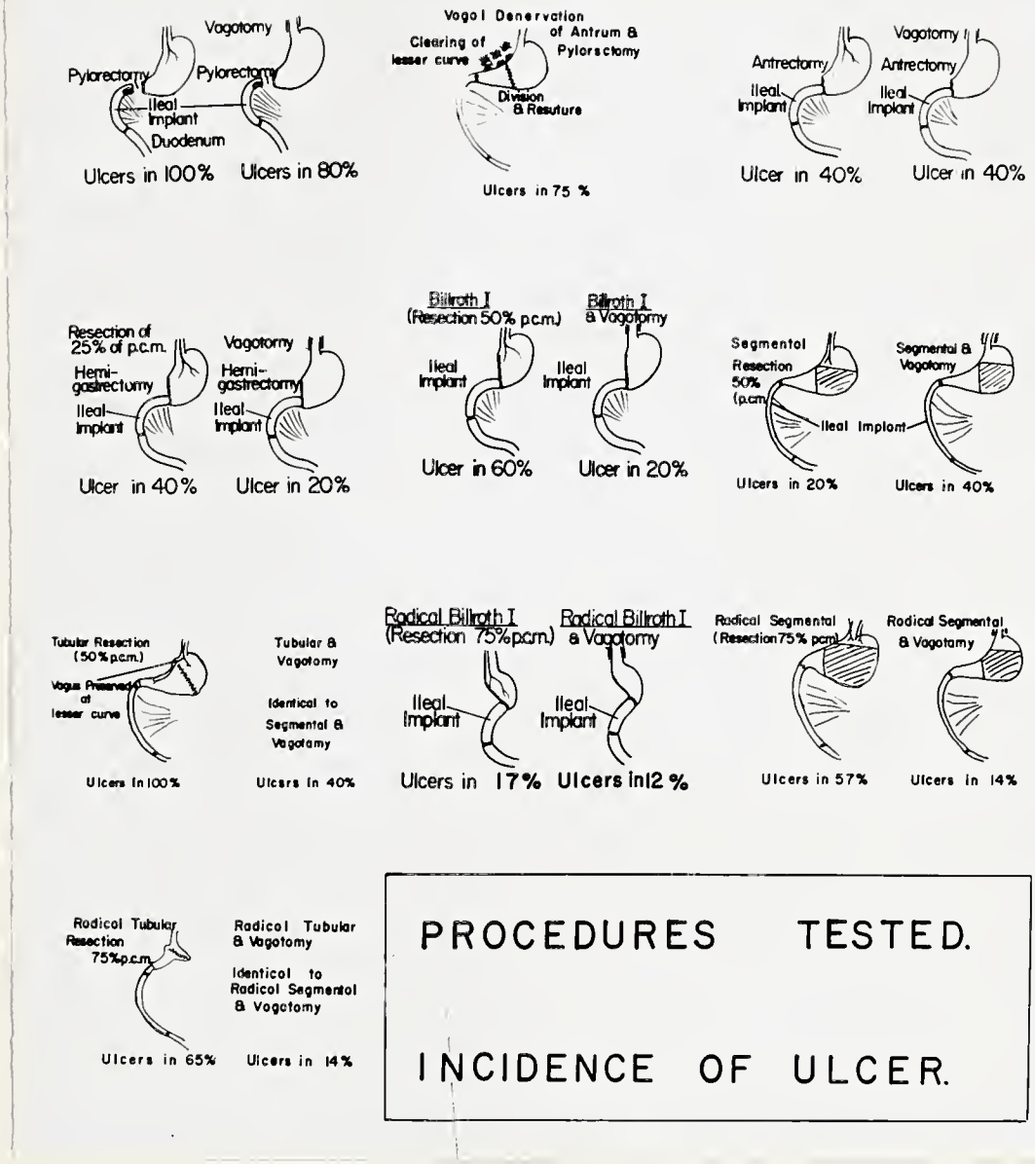
e) Meat and regular diet the seventh day.

Fluid and diet requirements were modified in some animals after assessing the condition of the animal. All animals were sacrificed after 90 - 100 days' time and postmortem examinations carried out. The weight of each animal before operation and at the time of sacrific was recorded. If any animal died during the postoperative period this animal was substituted by another. The animals tolerated the procedures well. Most of them were in good health at the time of sacrifice.

RESULTS

The incidence of ulceration associated with each of these procedures is shown in Figure 10. The gross appearance of ulcer in the ileal implant in some of these procedures is shown in Figure 11 a, b.

FIGURE 10



Procedures tested.

Incidence of ulcer.

FIGURE 11a

Gross appearance of ileal insert with ulcer -
Billroth I with 50% parietal cell mass excision

FIGURE 11b

Gross appearance of ileal insert with ulcer -
Segmental resection

The number of animals in each series is small and no statistically significant conclusions can be reached. In certain procedures where the incidence of ulceration was found to be 80 - 100% or 0% the results carry a certain weight. For example, pylorectomy with or without vagotomy (Fig. 10-1) showed the highest incidence of ulcer formation. This could be due to the factors considered in the pathogenesis of ulcer production in the implant. Tubular resection did not afford any protection against ulcer formation, whereas Williams' procedure of mucosal resection affords complete protection against ulcer formation.

When one considers the physiological variables the antrum, vagus and the parietal cell mass, the number of animals is significant and the comparisons are probably valid.

ANTRAL EFFECT

The antrum can be excised or retained, and if retained it can be vagally innervated or vagally denervated. Table IV compares the ulcerogenic effect between procedures in which the antrum is retained and identical procedures in which it is excised. A marked reduction in ulcer incidence occurs from 57 - 37% by antral excision. If the antrum is retained is its effect modified by vagal innervation? Table V compares the ulcerogenic effect in three series of animals -

a) Antrum preserved vagally innervated

b) Antrum preserved vagally denervated

c) Antrum excised

A collective study of these groups indicates that even though the antrum is in contact with acid secreting mucosa in all of these procedures there is a marked reduction in ulcer incidence when the antrum is vagally denervated, and a further reduction if it is excised. In Figure 12 these results are shown as a bar graph.

TABLE IV

ANTRAL EFFECT - OVERALL					
PROCEDURE	NO. OF DOGS	NO. OF ULCERS	PLUS ANTRECTOMY	NO. OF DOGS	NO. OF ULCERS
Pylorectomy (#1)	5	5	P. and Antrectomy (#4)	5	2
Vagal Den.of A. & P.(#2)	4	3	P. and Antrectomy (#4)	5	2
Pylorectomy & V. (#2)	5	4	P. & A. & V. (#5)	5	2
Segmental (#10)	5	1	Billroth I (#8)	5	3
Segmental & V. (#11)	5	2	Bill. I & V. (#9)	5	1
Tubular(#12)	5	5	Billroth I (#8)	5	3
Tubular & V. (#13)	5	2	Bill. 1 & V. (#9)	5	1
Radical Segmental (#16)	7	4	Rad. Bill. I (#14)	6	1
Rad. Segmental & V. (#17)	7	1	Rad. Bill. I & V. (#15)	8	1
Rad. Tubular (#18)	3	2	Rad. Billroth I (#14)	6	1
	51	29		55	17
Percent Ulcer	57		Percent Ulcer	31	

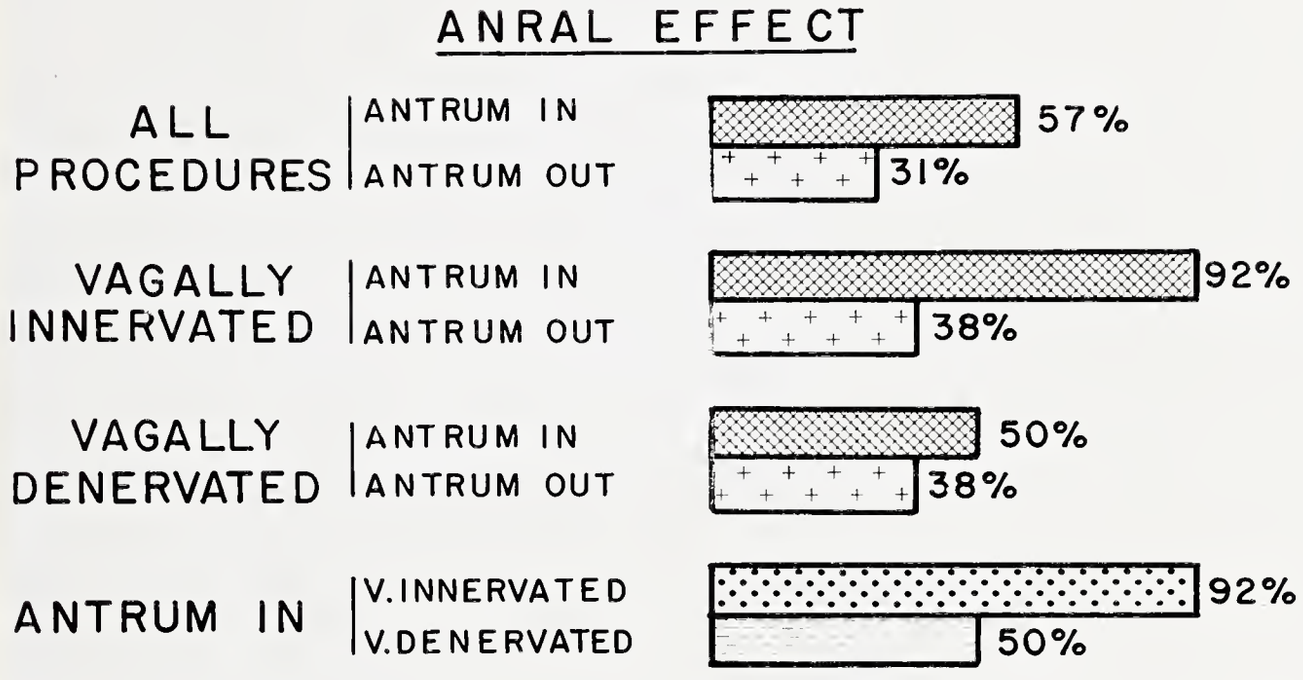
The effect of antrectomy in two comparable groups. In some procedures the antrum is vagally innervated, in others it is denervated.

TABLE V

	ANTRAL EFFECT								
	ANTRUM PRESERVED VAGALLY INNERVATED	NO. OF DOGS	NO. OF ULCERS	ANTRUM PRESERVED VAGALLY DENERVATED	NO. OF DOGS	NO. OF ULCERS	ANTRUM EXCISED	NO. OF DOGS	NO. OF ULCERS
A	Pylorectomy (Proc. #1)	5	5	Vagal Den. of Antrum & Pylor. (Proc. #3)	4	3	Antrectomy (Proc. #4)	5	2
B	Tubular (Proc. #12)	5	5	Segmental (Proc. #10)	5	1	Billroth I (Proc. #8)	5	3
C	Radical Tub. (Proc. #18)	3	2	Radical Seg. (Proc. #16)	7	4	Radical Bill. I (Proc. #14)	6	1
		13	12		16	8		16	6
	Percent Ulcer 92			Percent Ulcer 50			Percent Ulcer 38		

The incidence of ulcer when the antrum is vagally innervated, vagally denervated, and resected.

FIGURE 12



The effect of the antrum on the development of experimental ulcer.

VAGUS EFFECT

When the effect of vagotomy is studied in two comparable series (Table VI) the incidence of ulceration is almost halved by the addition of vagotomy. Is the reduction of ulcer incidence due to denervation of the remaining antrum or the denervation of the acid secreting parietal cell mass, or does it have its beneficial effect by a combination of these?

An analysis of the effect of vagotomy on acid secreting mucosa alone can be made by analyzing two comparable groups, those in which the antrum has been previously denervated by the primary procedure (Table VIIa) and those in which the antrum has previously been excised (Table VIIb). A study of these two groups together (Table VIIc) reveals that vagotomy of the parietal cell mass only reduces the incidence of ulceration slightly. In Figure 13 the effects of vagotomy are expressed as a bar graph.

PARIETAL CELL MASS EXCISION

There are two series (Table VIII a, b) in which the only variable is the percentage of parietal cell mass excised, enabling us to assess the effect of this factor on the incidence of ulceration. The incidence of ulceration was reduced by antrectomy; the incidence of ulceration was not reduced by the addition of 25% excision, nor by 50% excision, but it was reduced by 75% excision. Thus the reduction in parietal cell mass did not result in a striking decrease in ulcer formation unless the parietal cell mass excision exceeded 50%. The incidence of ulceration with a percentage of parietal cell mass excised is expressed diagramatically in Figure 14.

TABLE VI

VAGOTOMY EFFECT - OVERALL					
PROCEDURE	NO. OF DOGS	NO. OF ULCERS	PLUS VAGOTOMY	NO. OF DOGS	NO. OF ULCERS
Pylorectomy (#1)	5	5	Pylorectomy & V.(#2)	5	4
Antrectomy (#4)	5	2	Antrectomy & V. (#5)	5	2
Hemigastrectomy (#6)	5	2	Hemi. & V. (#7)	5	1
Billroth I (#8)	5	3	Bill. I & V. (#9)	5	1
Segmental (#10)	5	1	Seg. & V. (#11)	5	2
Tubular (#12)	5	5	Tub. & V. (#13)	5	2
Rad. Bill. I (#14)	6	1	Rad.Bill. I & V.(#15)	8	1
Rad. Seg. (#16)	7	4	Rad. Seg. & V. (#17)	7	1
Rad. Tub. (#18)	3	2	Rad. Tub. & V. (#19)	7	1
	46	25		52	15
Percent Ulcer	54		Percent Ulcer	29	

The effect of vagotomy in two comparable groups. In some procedures vagotomy exerts its effect on the parietal cell mass and the antrum - in others vagotomy only affects the parietal cell mass.

TABLE VII

TABLE V. EFFECT OF VAGOTOMY ON PARIETAL CELL MASS - ANTRUM PREVIOUSLY DENERVATED

ANTRUM VAG.DENERVATED P.C.M VAG. INNERVATED	NO. OF DOGS	NO. OF ULCERS	ADD - DENERVATION OF P.C.M.	NO. OF DOGS	NO. OF ULCERS
Vagal Den. of Antrum & Pylorectomy (#3)	4	3	Pylorectomy & V.(#2)	5	4
Segmental (#10)	5	1	Segmental & V. (#11)	5	2
Rad. Segmental (#16)	7	4	Rad. Seg. & V. (#17)	7	1
	16	8		17	7
Percent Ulcer	50		Percent Ulcer	41	

TABLE VI. EFFECT OF VAGOTOMY ON PARIETAL CELL MASS - ANTRUM PREVIOUSLY EXCISED

ANTRUM EXCISED P.C.M. INNERVATED	NO. OF DOGS	NO. OF ULCERS	ADD - DENERVATION OF P.C.M.	NO. OF DOGS	NO. OF ULCERS
Antrectomy (#4)	5	2	Antrectomy & V.(#5)	5	2
Hemigastrectomy (#6)	5	2	Hemi. & V.(#7)	5	1
Billroth I (#8)	5	3	Bill. I & V. (#9)	5	1
Radical Bill. I (#14)	6	1	Rad.Bill.I & V.(#15)	8	1
	21	8		23	5
Percent Ulcer	38		Percent Ulcer	21	

TABLE VII. EFFECT OF VAGOTOMY ON PARIETAL CELL MASS - COMBINED DATA

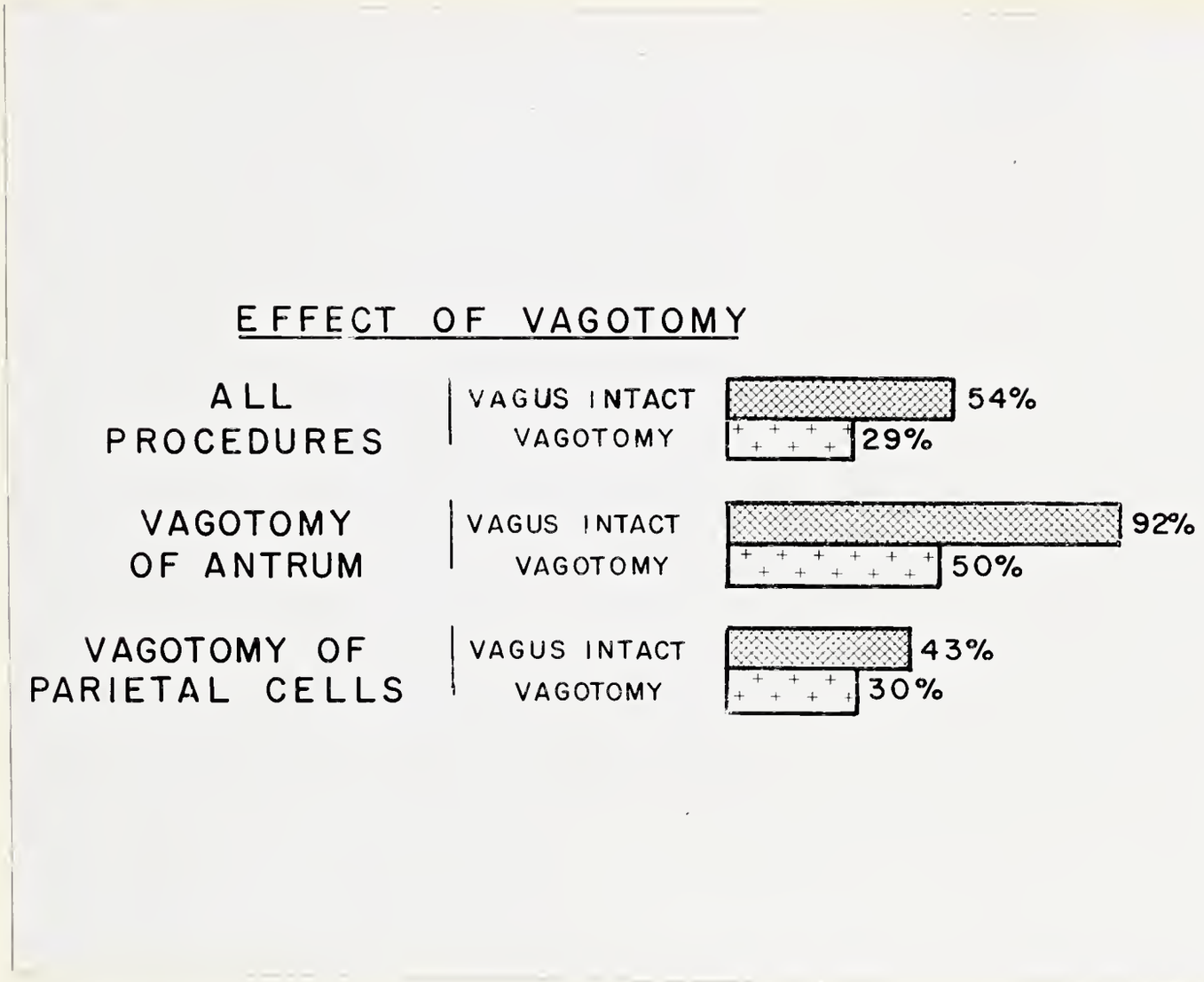
INNERVATED P.C.M.			DENERVATED P.C.M.		
	37	16		40	12
Percent Ulcer	43		Percent Ulcer	30	

a - The animals on the left have a vagally denervated antrum and a vagally innervated acid secreting mucosa. Those on the right have both areas denervated.

b - The animals on the left have had the antrum resected, but the parietal cell mass is vagally innervated. Those on the right have in addition vagal denervation of the parietal cell mass.

c - Data from a and b combined.

FIGURE 13



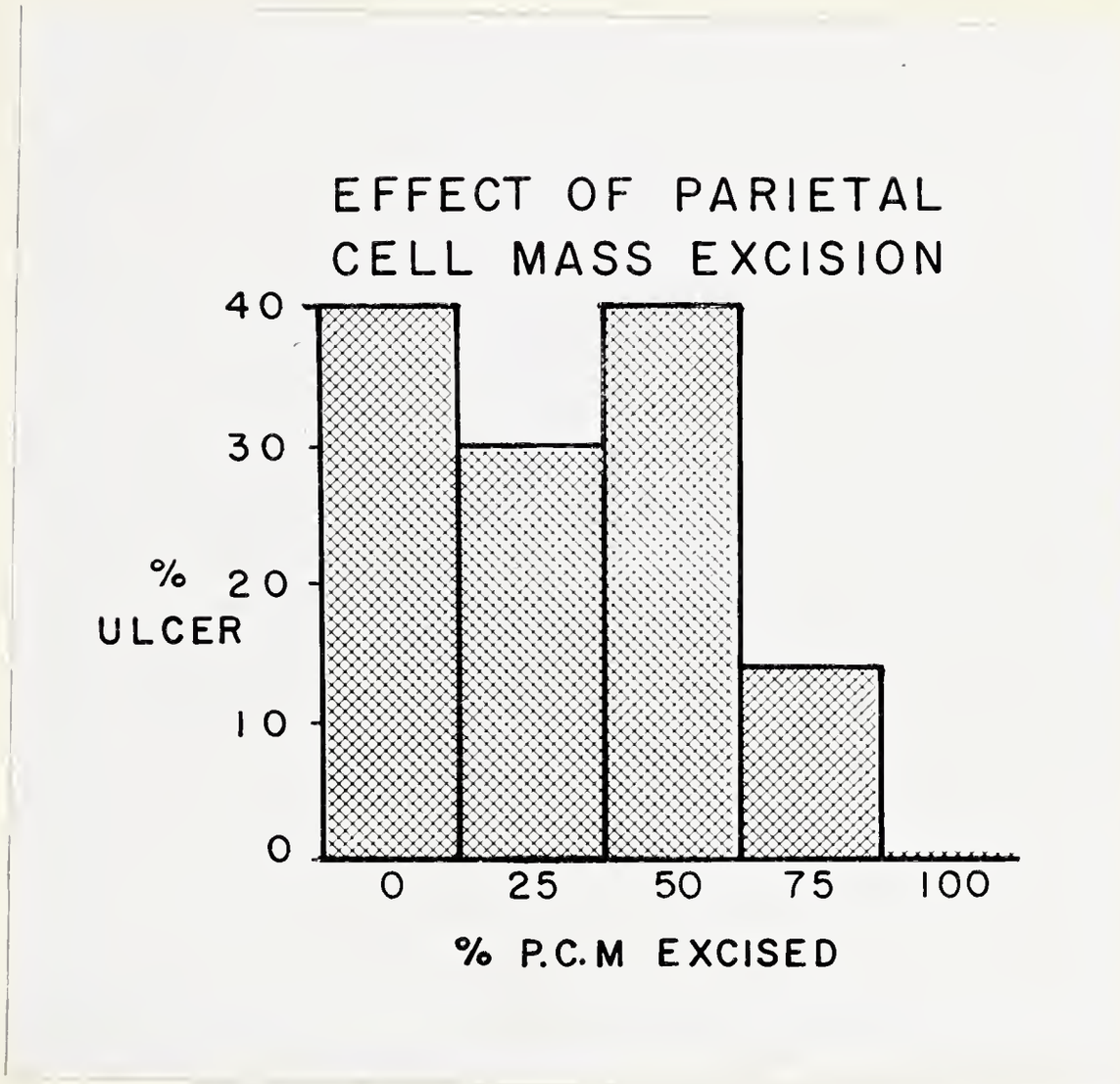
The effect of the vagus on the development of experimental ulcer.

TABLE VIII

	EFFECT OF PARIETAL CELL EXCISION											
	NO. P.C.M. EXCISION	NO. OF DOGS	NO. OF ULCERS	25% P.C.M. EXCISION	NO. OF DOGS	NO. OF ULCERS	50% P.C.M. EXCISION	NO. OF DOGS	NO. OF ULCERS	75% P.C.M. EXCISION	NO. OF DOGS	NO. OF ULCERS
A	Antrectomy (#4)	5	2	Hemigast. (#6)	5	2	Billroth I (#8)	5	3	Rad.Bill.I (#14)	6	1
B	Ant. & V. (#5)	5	2	Hemi. & V. (#7)	5	1	Bill.I & V. (#9)	5	1	Rad.BI & V. (#15)	8	1
		10	4		10	3		10	4		14	2
	Percent Ulcer 40			Percent Ulcer 30			Percent Ulcer 40			Percent Ulcer 14		

Effect of excision of the acid secreting portion of the stomach (parietal cell mass) on the subsequent development of ulcer.

FIGURE 14



The effect of excision of successive quarters of the parietal cell mass on the development of experimental ulcer.

DISCUSSION

a) Discussion of the Ileal Insert Procedure

In considering the pathogenesis of these experimental ulcers the following possibilities must be considered: -

1) The preparation increases acid secretion by eliminating or reducing the normal inhibitory effect of the duodenum, or by stimulating acid secretion in some manner. Thal[211] described an increase in pouch secretion in a similar procedure, but no ulcer developed. He used a jejunal rather than an ileal loop.

2) The reflux of bile, pancreatic secretion and succus entericus does not reach the proximal anastomosis of the implant to buffer successfully and to neutralize gastric acid. This probably depends on the length of the interposed segment of the ileum and reabsorption of the alkaline secretions by the implant.

3) The ileum lacks resistance to acid - peptic digestion. It has been reported that as the stomach is anastomosed to progressively lower segments of the intestinal tract, there is an increasing incidence of stomal ulcers, which has been attributed to a gradient of susceptibility to ulceration[164]. It has been shown, however, that in the absence of neutralizing secretions ulcers form with equal facility in the duodenum, jejunum, and ileum of the dog.

The reason for the occurrence of ulceration in the implant is probably the loss of alkaline secretions in the post-pyloric area, and also to the lack of resistance of the ileum to acid - peptic digestion.

b) Discussion of Results

Everyone is agreed that excision of the acid secreting portion of the stomach offers protection against ulceration, but there is a marked difference of opinion regarding the degree of protection which vagotomy affords. The demonstration of the autoregulatory role, which the antrum plays in acid production, has led to disagreement regarding whether it should be excised or preserved in duodenal ulcer surgery. Those who advocate its preservation cannot agree whether the vagal innervation of the antrum should be preserved or not.

Our studies on ulcer suggest that the antrum's ulcerogenic effect exceeds its autoregulatory effect, and that this is particularly true if it is vagally innervated. Vagotomy of the antrum reduces the incidence of ulceration to a greater degree than vagotomy of the parietal cell mass. This was more significant in vagotomy of the antrum than that of vagotomy of the parietal cell mass.

Everyone is agreed that excision of the acid secreting portion of the stomach offers protection against ulceration, but we were surprised to find that marked reduction in ulcer incidence occurs with radical excision of the parietal cell mass (75%).

Although there are many factors which enter into the decision for the choice of surgical procedures for duodenal ulcer, it is useful to know the advantages of each procedure in the prevention of ulcer recurrence.

When the antrum is present vagotomy has its greatest influence in reducing ulceration by denervation of the antrum rather than by denervation of the parietal cell mass. Excision of acid secreting mucosa in segmental resection is identical to that in tubular resection, and in both instances the antrum is preserved. In tubular resection, however, the vagal denervation to the antrum is maintained, and this might well explain the higher incidence of ulceration following this procedure.

CONCLUSIONS

The effectiveness of various surgical procedures in reducing the incidence of experimental ulcer in 90 dogs has been studied. Those factors which control acid secretion have been analyzed, and the following conclusions appear warranted: -

1) With the exception of complete excision of the gastric mucous membrane, none of the presently employed procedures for duodenal ulcer completely protected the animals against the development of ulceration.
2) The ulcerogenic properties of the antrum exceed its autoregulatory role. Significant reduction in ulcer incidence occurs if it is excised. If the antrum is retained its ulcerogenic properties are much reduced by its vagal denervation.
3) Vagotomy reduces the incidence of ulceration by almost one-half. This is more significant after vagotomy of the antrum than after vagotomy of the parietal cell mass.
4) Resection of the parietal cell mass is effective in preventing ulceration. The effect is only significant if the excision exceeds 50%.

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TABLE IX - Animal experiments performed by the author

No. of Dog	Procedure	Sex	Date of Operation	Date of Sacrifice	Pre-op. Wt.	Post-op. Wt.	Complication	Ulcer
130	Tubular - Resection	M	13-1-1959	12-4-1959	16.5 K	16 K		+
150	"	F	16-1-1959		20.5 K		Died	-
154	"	M	19-1-1959	1-5-1959	18 K	18 K		+
131	"	M	10-2-1959		14 K		Died	
136	"	F	11-2-1959 I 3-3-1959 II		21 K		Pregnancy & intestinal obstruction	
148	"	M	12-2-1959	17-6-1959	11 K	10 K		+
137	"	F	13-2-1959	17-6-1959	10 K	9 K		+
511	"	F	22-4-1959	1-8-1959	13 K	10 K		+
157	Segmental Resection	M	21-1-1959	2-4-1959	12½ K	13 K		-

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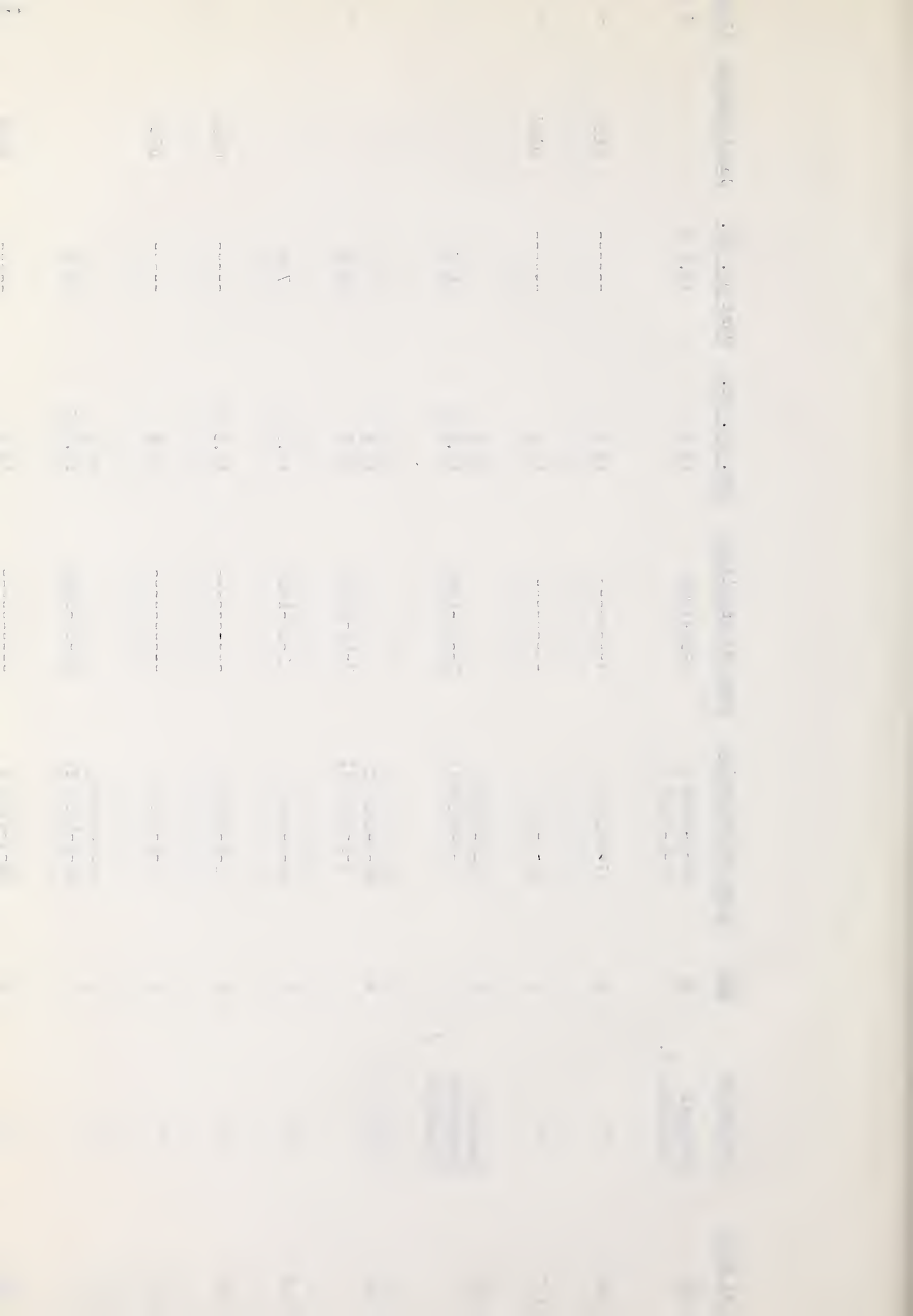
No. of Dog	Procedure	Sex	Date of Operation	Date of Sacrifice	Pre. op. wt.	Post op. wt.	Complication	Ulcer
134	Segmental-Resection	M	2-2-1959 I 3-3-1959 II	2-6-1959	17 K	17 K		+
166	"	F	3-2-1959 I 14-4-1959 II	6-8-1959	29 K	28 K		–
161	"	M	5-2-1959 I 4-3-1959 II	4-6-1959	24 K 21 K	21 K		–
165	"	M	16-2-1959 I 13-3-1959 II	7-7-1959	10 K	10 K		–
147	"	M	20-2-1959 I 16-4-1959 II	_____	15.5 K	------	Died	
124	"	F	22-2-1959 I 17-4-1959 II	---------	23 K	------	Died	
514	"	F	21-2-1959	---------	19.5 K	------	Died	
519	Segmental Resection Vagotomy	M	20-5-1959 I 30-6-1959 II	3-10-1959	15.5 K 14 K	14 K		–
520	"	M	21-5-1959 I 2-7-1959 II	24-11-1959	21.5 K 15.5 K	16 K		–

No. of Dog	Procedure	Sex	Date of Operation	Date of Sacrifice	Pre. op. wt.	Post op. wt.	Complication	Ulcer
113	Segmental Resection Vagotomy	M	23-2-1959 I 24-2-1959 II	3-8-1959	20 K 21 K	20 K		+
162	"	F	18-2-1959	3-6-1959	10 K	10 K	Intestinal Obstruction	+
164	"	M	17-2-1959 I	--------	11.5 K	----	Died, Hair bolus obstruction	–
138	"	M	18-2-1959 I 16-2-1959 II	--------	11 K	----	Died	–
163	"	M	19-2-1959 I 17-4-1959 II	--------	14.5 K 14 K	----	Died	–
515	"	M	28-4-1959	9-8-1959	13 K	12.5 K		–
129	Billroth I 50% P.C.M.	M	9-1-1959	9-5-1959	16 K	15 K		+
158	"	M	22-1-1959	1-5-1959	11.5K	9 K		+
168	"	M	26-1-1959	1-5-1959	15 K	13.5 K		–

No. of Dog	Procedure	Sex	Date of Operation	Date of Sacrifice	Pre. op. wt.	Post op. wt.	Complication	Ulcer
528	Billroth I 50% P.C.M.	F	3-6-1959	3-10-1959	11.5 K	10 K		—
132	"	M	29-1-1959	----------	11 K	----	Died	—
133	"	M	30-1-1959	1-5-1959	15 K	14.5 K		+
128	"	F	30-1-1959	---------	12.5 K	------	Died	—
160	Billroth I 50% P.C.M. V	M	23-1-1959	---------	14.5 K	------	Died	—
170	"	F	24-1-1959	_____	14 K	------	Died	—
167	"	M	26-1-1959	1-5-1959	17 K	13.5 K		+
111	"	M	28-1-1959	---------	13.5 K	------	Died	—
135	"	F	3-2-1959	29-6-1959	21 K	20 K		—
149	"	F	6-2-1959	29-6-1959	14 K	13.5 K	Pregnancy	—

No. of Dog.	Procedure	Sex	Date of Operation	Date of Sacrifice	Pre. op. wt.	Post op. wt.	Complication	Ulcer
123	Billroth I 50% P.C.M. V	M	25-2-1959	29-6-1959	17.5 K	17 K		–
146	"	M	26-2-1959	--------	16.5 K	----	Lost in form	–
144	"	M	27-2-1959	29-6-1959	17 K	15 K		–
114	"	M	2-3-1959	29-6-1959	17 K	16.5 K		–
122	Redical Segmental R.	F	19-3-1959 I 8-5-1959 II	7-9-1959	13.5 K 11.5 K	11 K		+
115	"	F	20-3-1959 I 6-5-1959 II	7-9-1959	13 K 12 K	12 K		–
120	"	M	23-3-1959 I 30-4-1959 II	3-10-1959	14.5 K	15 K		+
503	"	M	2-4-1959	3-10-1959	15.5 K	16 K		–
522	"	F	26-5-1959 I 3-7-1959 II	12-11-1959	21.5 K 16.5 K	15 K		–
523	"	M	27-5-1959 I 30-6-1959 II	3-10-1959	16.5 K	15 K		+

No. of Dogs	Procedure	Sex	Date of Operation	Date of Sacrifice	Pre. op. wt.	Post op. wt.	Complication	Ulcer
525	Redical Segmental R.	M	29-5-1959 I 25-6-1959 II	3-10-1959	15 K	14.5 K		+
119	"	M	27-6-1959	---------	18 K	------	Died	-
117	"	F	27-6-1959	---------	12 K	------	Died	-
116	Redical Segmental Resection V	F	25-3-1959 I 4-5-1959 II	30-10-1959	18 K 11.5 K	11 K		+
118	"	M	26-3-1959 I 5-5-1959 II	3-10-1959	12 K 12 K	10 K		-
507	"	F	20-4-1959	3-10-1959	18.5 K	17 K		-
510	"	M	21-4-1959	----------	14.5 K	-----	Died	-
512	"	M	23-4-1959	----------	16 K	-----	Died	-
516	"	F	29-4-1959 I 18-6-1959 II	19-10-1959	14 K 12.5 K	12 K		-
524	"	F	28-5-1959 I 25-6-1959 II	----------	10 K	-----	Died	-



No. of Dog	Procedure	Sex	Date of Operation	Date of Sacrifice	Pre. op. wt.	Post op. wt.	Complication	Ulcer
526	Redical Segmental Resection V	M	1-6-1959 I 25-6-1959 II	--------	10.5 K	----	Died	—
580	"	M	1-5-1959 I 25-5-1959 II	19-10-1959	17.5 K	16 K		—
582	"	M	1-6-1959 I 25-6-1959 II	19-10-1959	16 K	15 K		—
583	"	M	28-5-1959 I 25-6-1959 II	19-10-1959	12.5 K	13 K		—
139	Radical Billroth I 75% P.C.M.	M	6-3-1959	12-7-1959	15 K	15.5 K		—
140	"	M	9-3-1959	12-7-1959	18.5 K	16 K		—
141	"	F	10-3-1959	19-7-1959	18.5 K	17 K		+
142	"	M	13-3-1959	12-7-1959	15 K	15 K		—
143	"	F	16-3-1959	--------	17 K	----	Died	—

No. of Dog	Procedure	Sex	Date of Operation	Date of Sacrifice	Pre. op. wt.	Post op. wt.	Complication	Ulcer
171	Radical Billroth I 75% P.C.M.	M	17-3-1959	12-7-1959	17.5 K	16.5 K		—
521	"	M	22-5-1959	---------	16.5K	------	Lost in Form	—
527	"	M	2-6-1959	---------	16.5 K	------	Died	—
505	"	F	10-4-1959	16-8-1959	18 K	18 K		—
529	"	F	5-6-1959	---------	16.5 K	----	Died	—
530	"	M	8-6-1959	---------	15 K	-----	Died, Hair bolus obstruction	
531	"	M	9-6-1959	---------	14.5 K	-----	Lost in Form	
501	Radical Billroth I 75% P.C.M. V	M	6-4-1959	2-9-1959	16 K	15 K		—
502	"	F	7-4-1959	2-9-1959	19 K	18 K		—
500	"	M	8-4-1959	2-9-1959	13.5 K	14.5 K		+

No. of Dog	Procedure	Sex	Date of Operation	Date of Sacrifice	Pre. op. wt.	Post op. wt.	Complication	Ulcer
504	Radical Billroth I 75% P.C.M. V	F	9-4-1959	2-9-1959	18.5 K	18 K		—
506	"	F	13-4-1959	2-9-1959	19 K	17 K		—
532	"	M	11-6-1959	7-10-1959	16 K	15.5 K		—
533	"	M	15-6-1959	7-10-1959	20.5 K	19 K		—
534	"	M	17-6-1959	7-10-1959	24 K	22 K		—

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